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# ACUTE ESOPHAGITIS IN INFANTS

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FEW INVESTIGATORS have directed their attention toward the frequent occurrence of acute ulcerative esophagitis. Among them, however, several have been impressed with the fact that the lesion frequently occurs in adults (Vinson and Butt [1]; Olsen [2]). Billard [3] noted more than one hundred years ago that esophagitis was common in infants. He explained this by the existence of a predisposing factor, namely, the marked congestion of the blood vessels in the wall of the esophagus, which he observed in almost every newborn infant examined at autopsy. Diamantopoulos [4] gave a good review of the subject of ulcerative esophagitis in the newborn, compiling 12 cases from the literature and describing his own observation of a dramatic case in which a 3 day old infant was found in a pool of blood. It continued to bleed from the mouth and died on the same day. At autopsy the esophagus showed an ulcer near the cardia, with a large clot of blood adherent to it. No ulcers existed in the stomach or the intestine and no focus of infection was detected. More recently Ebbs [5] and Reye [6] described 28 and 10 cases, respectively, in which esophagitis was found in newborn infants at autopsies. Thrush (moniliasis) was present in a high proportion of these infants. Brown and Kellert [7] have stated that in newborn infants ulcers occur much more frequently in the stomach or the duodenum than in the esophagus.

The present investigation of esophagitis in infancy is based on 52 cases found in a series of 310 autopsies. In each instance the tentative

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1. Vinson, P. P., and Butt, H. R.: J. A. M. A. **106**:994, 1936.
2. Olsen, A. M.: Surg., Gynec. & Obst. **86**:372, 1948.
3. Billard, C. M.: Traité de maladies des enfants, Paris, J. B. Baillière, 1833.
4. Diamantopoulos, S.: Ztschr. f. Kinderh. **42**:606, 1926.
5. Ebbs, J. H.: Arch. Dis. Childhood **13**:211, 1938.
6. Reye, D.: M. J. Australia **2**:673, 1941.
7. Brown, M. M., and Kellert, E.: New England J. Med. **209**:202, 1933.

diagnosis was made at autopsy and confirmed by the histologic criteria to be described in subsequent pages. Statistical data on the incidence are presented in table 1. For the purpose of statistical evaluation, the material has been divided into two groups obtained during successive periods of time.

During the first period no special attention was paid to changes in the esophagus, whereas careful observations were made during the second period. The esophagus was opened and inspected in all cases; however, in the old series we were not aware of the high incidence and possible significance of esophagitis, and in many instances no sections were taken for microscopic examination. In the new series, on the other hand, the esophagus was examined more carefully grossly and microscopically. It will be seen from table 1 that the incidence of esophagitis is higher in the new series, and since there is no reason to assume that the actual incidence was different, one is led to believe that the difference is due to the attention given the esophagus at autopsy.

TABLE 1.—*Incidence of Esophagitis in 310 Consecutive Autopsies on Infants*

| | Old Series | | New Series | | Total | |
|---|---|---|---|---|---|---|
| Age, Months | Autopsies | Number with Esophagitis | Autopsies | Number with Esophagitis | Autopsies | Number with Esophagitis |
| 0-½ | 101 | 12 | 98 | 20 | 199 | 32 |
| ½-1 | 18 | 2 | 9 | 3 | 27 | 5 |
| 1-2 | 23 | 0 | 11 | 4 | 34 | 4 |
| 2-6 | 12 | 5 | 22 | 6 | 34 | 9 |
| 6-12 | 7 | 1 | 9 | 0 | 16 | 1 |
| Total | 161 | 19 | 149 | 33 | 310 | 52 |

Moreover, facilities for more extensive microscopic examination of all organs were available with the second series, so that data on the incidence of esophagitis, as well as on any association of this and other pathologic conditions, are more reliable for the new series than for the old one. Even though it may be assumed that several cases of esophagitis were missed in the old series, the over-all incidence is high, and substantially higher than that of 7.02 per cent given by Vinson and Butt [1] for a series of autopsies on persons of all ages.

## DESCRIPTION OF FINDINGS

Often the tentative diagnosis of esophagitis can be made at autopsy when the mucosa is greatly hyperemic and shows ulcers or has a dull sheen. Microscopic examination confirmed the diagnosis in almost all instances, and also led to the discovery of additional cases. During the period in which the "new series" of cases was collected, a cross section at the level of the larynx and a longitudinal section of the cardia and adjoining portion of the esophagus were taken at all autopsies on infants; additional sections were made of areas suspected to be inflamed.

Ulcers were found, grossly as well as microscopically, in the great majority of all cases in which esophageal lesions were noted. They extended into the propria (figs. 12 and 14) and in several instances into the submucosa (figs. 2, 4, 6, 7, and 10). The muscularis occasionally showed severe congestion and hemorrhage (figs. 6 and 7) or leukocytic infiltration (figs. 4 and 6). In many instances the ulcerated and adjoining portions of the mucosa were covered with a layer of

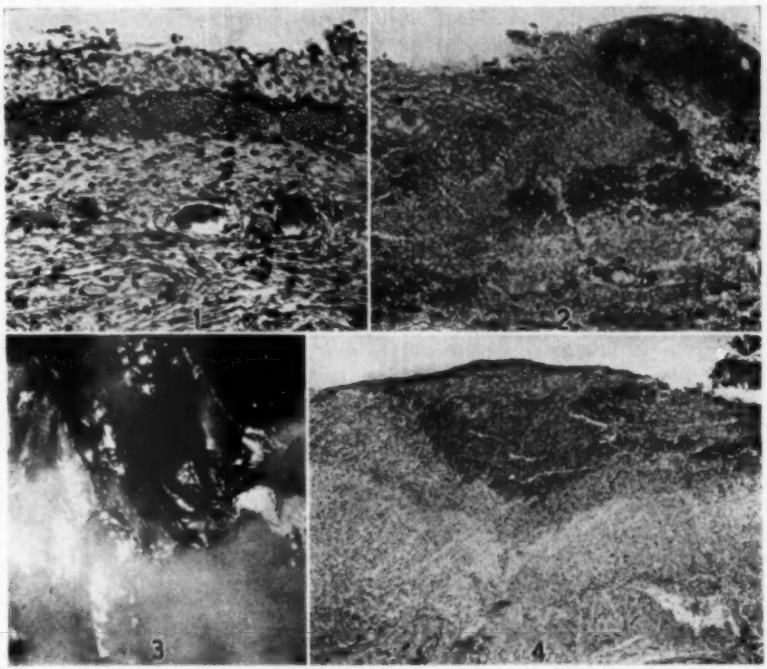


Fig. 1 (case 4).—Severe congestion of blood vessels just beneath the epithelium.
Fig. 2 (case 17).—Border of a deep ulcer, with hemorrhage into the adjacent mucosa (right side of figure).
Fig. 3 (case 19).—Region of the cardia. The esophagus is dark red and shows ulcerations. The lesion ends sharply at the transition to gastric mucosa.
Fig. 4 (case 19).—Section of the area shown in figure 3, with a dense accumulation of leukocytes in the submucosa. The mucosa is ulcerated.

necrotic débris, fibrin, leukocytes and in some cases micro-organisms (fig. 12). Uusually the mucosa near the ulcers and often also other parts of the mucosa were severely infiltrated with polymorphonuclear leukocytes. In no case was the existence of esophagitis recognized in the absence of such infiltration.

In many areas which were inflamed but not ulcerated the epithelium was thin, consisting of one or two layers of cells (fig. 14). This may be an indication of regeneration of the epithelium.

A peculiar type of hyperemia was present in the propria in many infants found to have esophagitis, and also in some stillborn and live-born infants in whom esophagitis was not diagnosed because of the absence of leukocytic infiltration. A layer of capillaries just under the epithelium was so severely distended with blood that one might believe at first glance that a continuous layer of blood separated the epithelium from the propria (fig. 1). In some newborn infants this was part of the severe venous congestion which characteristically occurs in the thoracic viscera in asphyxia; in others the hyperemia was obviously part of the inflammatory reaction of esophagitis. In some cases hyperemia was probably an early stage of esophagitis; whether or not asphyxial hyperemia may lead or predispose to esophagitis has not been determined; the possible relationship of asphyxia and esophagitis will be discussed later.

The commonest localization of esophageal ulcers was just above the cardia. This area was, as a rule, most severely affected when esophagitis extended throughout most of the length of the organ. Inflammation ended abruptly where gastric mucosa began (fig. 3); the latter was never affected by an extension of the esophageal lesion. In some cases ulcers were found at the level of the larynx, and seldom were ulcers scattered throughout the length of the esophagus (fig. 8).

Occasionally clotted blood was found adhering to the surface of an ulcer (figs. 9 and 10), and in 1 case a cast of such blood was free in the lumen (fig. 13). In many instances the stomach contained brown flakes suggestive of transformed blood.

In the following report of cases the pathologic conditions alone will be enumerated unless some feature of particular interest warrants a detailed description of clinical and pathologic observations. Certain data are summarized in table 2.

1. A boy was delivered spontaneously and weighed 2,500 Gm.; his cry was weak and his respirations were shallow. Ten hours after birth he became cyanotic, ceased breathing and died in spite of efforts at resuscitation. Autopsy revealed: bronchopneumonia; dilatation of the heart; general venous congestion; petechial hemorrhages in the brain; necrosis in the coronary arteries; aspirated vernix; esophagitis; cloudy swelling of liver and kidneys.

2. A girl 12 hours old: prematurity; aspiration of amniotic fluid; hemorrhages in epicardium and thymus; esophagitis.

3. A 12 hour boy: prematurity; atelectasis; erosions of the stomach; esophagitis; hemorrhages in the epicardium.

4. This was the fourth pregnancy and lasted seven months. After twelve hours of labor, twins were delivered spontaneously. The second twin, a boy, weighed 1,130 Gm. In spite of tracheal aspiration and the administration of a 25 per cent

nikethamide solution, the infant died after six and a half hours. Autopsy revealed: general venous congestion; atelectasis; hemorrhages in epicardium and myocardium; hematoma of the liver; esophagitis. Microscopically, the blood vessels of the propria were greatly dilated (fig. 1). Just above the cardia there was a small ulcer and around it there was leukocytic infiltration.

5. A boy, the first child, was delivered at term by cesarean section after thirty-six hours of labor. He weighed 4,170 Gm. His respiration was delayed and obstructed and he was cyanotic. Tracheal aspiration and nikethamide stimulation were used. The baby was thought to have aspirated infected amniotic fluid. Resuscitation was attempted terminally with the Flagg apparatus, but the infant died twenty-one hours after birth. Autopsy revealed: aspiration of vernix and meconium; bronchopneumonia; esophagitis; acute pancreatitis; necrosis of coronary arteries; fatty liver; jaundice; edema of the brain.

TABLE 2.—*Summary of Clinical and Pathologic Data on 52 Cases of Esophagitis*

| Age, months | 0-½ | ½-1 | 1-2 | 2-6 | 6-12 | Total |
|---|---|---|---|---|---|---|
| Number of cases | 33 | 5 | 4 | 9 | 1 | 52 |
| **Clinical Findings** * | | | | | | |
| Prematurity | 14 | 1 | 2 | 4 | .. | 21 |
| Neonatal asphyxia | 19 | .. | .. | .. | .. | 19 |
| Tracheal aspiration | 17 | .. | .. | .. | .. | 17 |
| Gavage feeding | 6 | 1 | 1 | 4 | 0 | 12 |
| Wangensteen suction | 2 | 1 | 0 | 0 | 0 | 3 |
| Vomiting with blood | 15 | 2 | 0 | 2 | 0 | 17 |
| Vomiting without blood | 7 | 1 | 2 | 6 | 1 | 17 |
| Melena | 2 | 0 | 0 | 1 | 0 | 3 |
| Congenital syphilis (confirmed at autopsy) | 0 | 0 | 2 | 3 | 0 | 5 |
| **Pathologic Changes** * | | | | | | |
| Signs of asphyxia | 14 | .. | .. | .. | .. | 14 |
| Intracranial hemorrhage | 11 | 1 | 0 | 0 | 0 | 12 |
| Cerebral edema | 3 | 1 | 1 | 1 | 0 | 6 |
| Kernicterus | 5 | 0 | 0 | 0 | 0 | 5 |
| Degeneration of parenchymatous organs | 6 | 0 | 0 | 2 | 0 | 8 |
| Jaundice | 11 | 1 | 1 | 2 | 0 | 15 |
| Gastritis, erosions | 6 | 0 | 1 | 0 | 0 | 7 |
| Enteritis and/or peritonitis | 4 | 1 | 0 | 4 | 0 | 9 |
| Bronchopneumonia | 16 | 2 | 3 | 5 | 0 | 26 |
| Malformation of esophagus | 1 | 0 | 0 | 0 | 0 | 1 |
| Perforation into pleural cavity | 2 | 0 | 0 | 0 | 0 | 2 |

* Where there is no entry of number of cases no information has been sought.

6. A girl, 1 day old: prematurity; atelectasis; esophagitis.

7. The mother was admitted in labor two days before delivery and allegedly had been in labor two days before admission. On the evening before delivery her temperature was 102 F. No data on the course of this 1 day old girl are available. At autopsy the body weighed 3,300 Gm. The findings included: aspiration of meconium; intraventricular and subarachnoid hemorrhage; esophagitis; hemorrhages in the epicardium; dilatation of the heart; necrosis of coronary and hepatic arteries; fatty liver. The esophagus showed a dark hemorrhagic discoloration of the mucosa in its lower half. Microscopically, there was marked edema of the mucosa with greatly dilated vessels and areas of hemorrhage. There was a moderate mobilization of polymorphonuclear leukocytes. The muscularis was destroyed by hemorrhage in many areas. A few small ulcerations were present in the mucosa. Bacterial stains revealed no micro-organisms.

8. A 30 hour boy: prematurity; aspiration of contents of the amniotic sac; bronchopneumonia; general venous congestion; hypertrophy and dilatation of the heart; esophagitis; necrosis of hepatic arteries; dehydration.

9. A 30 hour girl: prematurity; aspiration of meconium; general venous congestion; hemorrhages in pleura and epicardium; necrosis of the coronary arteries; esophagitis; conjunctivitis; fatty liver; swelling of the brain.

10. After a thirty-five week gestation and a seven hour labor, during which the cord prolapsed twenty minutes before delivery, a girl was delivered by low forceps. Her respiration was delayed and shallow and she was cyanotic. Treatment consisted of aspiration, administration of positive pressure oxygen and continuous artificial respiration for one and one half hours. The temperature rose to 103 F. There was bright red blood on the diaper, and bloody mucus was coming from the trachea. The baby died thirty-five hours after birth. At autopsy the body weighed 2,640 Gm. The findings were: bronchopneumonia; esophagitis; general venous congestion; bilateral pleural effusion; fatty liver; intraventricular hemorrhage.

11. A 2 day boy: prematurity; bronchopneumonia; fracture of the right parietal bone; focal hemorrhages in the brain; esophagitis.

12. After a forty week gestation and a seventeen hour labor, during which meconium-stained amniotic fluid was observed, a girl was delivered by low forceps. Her respiration was obstructed, her color cyanotic and her general condition poor. The larynx was aspirated, and gavage feedings were given. Coffee-ground-like material was seen in the nares before death, which occurred thirty-seven hours after birth. At autopsy the body weighed 3,580 Gm. The findings included: aspiration of contents of the amniotic sac; bronchopneumonia; dilatation of the heart; hemorrhages in the epicardium; necrosis of the coronary arteries; esophagitis; erosions of the stomach; congestion and edema of the brain; minimal subarachnoid hemorrhages; bilateral clubfoot.

13. A thirty-eight hour girl: volvulus of the small intestine with perforation and peritonitis; aspiration of contents of the amniotic sac; bronchopneumonia; esophagitis; follicular cysts of the ovaries; minimal subdural hemorrhage. Microscopically, there was a suggestion of early cystic fibrosis of the pancreas.

14. A boy was born after thirty-eight weeks of gestation and a four hour labor; he weighed 2,530 Gm. He was cyanotic at birth but improved after administration of oxygen. One day after birth he was jaundiced; the liver was palpable, and the skin showed many petechial hemorrhages. A blood smear revealed numerous nucleated erythrocytes and absence of thrombocytes. There were 1,080,000 erythrocytes per cubic millimeter of blood. The baby died two days after birth with the clinical diagnosis of erythroblastosis fetalis. Autopsy revealed: enlargement of liver and spleen with extramedullary hemopoiesis; jaundice; kernicterus; bronchopneumonia; esophagitis; hemorrhages in the epicardium.

15. A 2 day girl: prematurity; hyaline membranes in bronchioles; atelectasis; hemorrhages in epicardium and thymus; esophagitis.

16. A 2 day boy: prematurity; focal defect of the muscularis of the small intestine with enteritis, perforation and peritonitis; jaundice; esophagitis; immaturity of the lung tissue; thrombosis of a renal vein.

17. A 2,820 Gm. boy was delivered at term after twenty hours of labor, which was difficult because of a generally contracted pelvis. Respiration was shallow and the cry weak. The baby died two days after birth. Autopsy revealed: esophagitis with rupture into the right pleural cavity and pleuritis; shift of the mediastinum to the left; aspiration of vernix; interstitial emphysema; hemorrhages in the epicardium; subdural and subarachnoid hemorrhage. The right pleural cavity contained about 10 cc. of pale yellow, turbid fluid with large flakes of loose yellowish curdlike material. A similar material covered the pleural surfaces. The

base of the lung was attached to the diaphragm by a layer of yellowish fibrin. The lung was collapsed. Behind the hilus there was an opening, measuring 2 by 5 mm., which led into the esophagus. The esophagus was lined near its upper and lower ends with a pale, glistening mucosa. The greater, intermediate part was dilated and had a greatest circumference of 18 mm. Its mucosa was dark red and showed on the right side the aforementioned opening into the pleural cavity. Microscopically, this part of the esophagus showed extensive hemorrhage into the mucosa. The epithelial lining was thin. There was an ulceration which in the area examined penetrated almost all layers of the wall (fig. 2). The adjacent tissue was severely infiltrated by polymorphonuclear leukocytes. Another section showed diffuse edema, hyperemia and moderate leukocytic infiltration of all layers of the wall. Many clusters of gram-positive cocci were demonstrated on the surface of the inflamed tissue.

18. A 2 day girl: aspiration of vernix; interstitial pneumonia; tears of the tentorium; subdural and subarachnoid hemorrhage; subperiosteal hemorrhage of the skull; dilatation of the heart; esophagitis; moderate degeneration of the liver; jaundice; edema; mild ascites.

19. A boy weighing 2,640 Gm. was born spontaneously at term after twenty-four hours of labor. He was the twelfth child of an Rh-negative mother. The respiration was spontaneous and the color pale. There were petechial hemorrhages; the baby bled from the mouth and voided blood-tinged urine. It received a transfusion of 35 cc. and died fifty-two hours after birth, with the diagnosis of erythroblastosis. Autopsy revealed: jaundice; enlargement of liver and spleen; hemopoiesis in liver, spleen, pancreas, adrenal glands, kidneys and testes; hemosiderosis of liver and spleen; kernicterus; aspiration of amniotic fluid and blood; hyaline membranes in bronchioles; bronchopneumonia; hemorrhages in thymus, lungs, bladder, epicardium, skeletal muscles and stomach; esophagitis; erosions in the stomach. The mucosa of the esophagus was dark red in the upper half. In the lower half (fig. 3), which was somewhat dilated, it was covered by a dull opaque membrane which showed icteric coloration. Most of the esophagus was devoid of epithelium. The propria and submucosa were infiltrated by large numbers of polymorphonuclear leukocytes, and the superficial layers were necrotic. In some portions the leukocytes formed very dense, abscess-like accumulations (fig. 4).

20. A 2½ day girl: prematurity; aspiration of vernix; bronchopneumonia; general congestion and cyanosis; esophagitis; focal cerebral hemorrhage; thickening of shaft of femur (? syphilis).

21. A 3 day boy: laparotomy wound with exteriorized colon; fibrinous peritonitis; membranous occlusion of the sigmoid; esophagitis; partial pulmonary atelectasis.

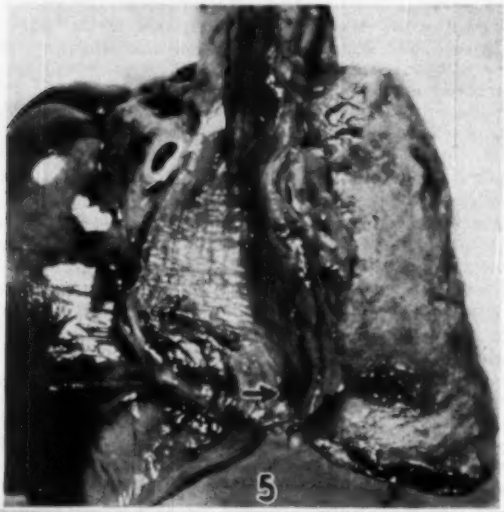
22. A 3 day girl: erythroblastosis (jaundice, enlargement of liver and spleen, and kernicterus); bronchopneumonia; esophagitis; general venous congestion.

23. A 3 day girl: moderate enlargement of liver and spleen without extramedullary hemopoiesis; diffuse interstitial pneumonia; atelectasis; esophagitis (clinically, erythroblastosis).

24. A 3 day boy: bronchopneumonia; tear of the falx cerebri; subdural and subarachnoid hemorrhage; focal meningitis; esophagitis; jaundice; stenosis of the left ureter with hydronephrosis.

25. A boy weighing 3,120 Gm. was born spontaneously at term after nineteen hours of labor. The respiration was normal and the cry weak. Three days after birth there was sudden respiratory difficulty. Roentgen examination revealed

hydropneumothorax on the right side. The baby became dehydrated, went rapidly downhill and died on the same day. Autopsy revealed esophagitis with perforation into the right pleural cavity (fig. 5). There were fibrinopurulent pleuritis and



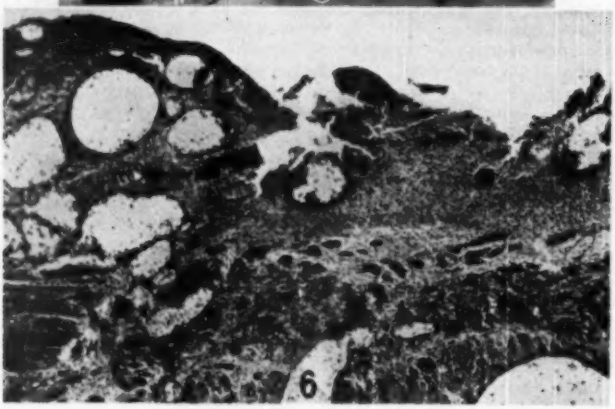




Fig. 5 (case 25).—Posterior view of the thoracic viscera. The esophagus is dilated and ulcerated, with a perforation (arrow) into the right pleural cavity. The right lung is covered with a fibrinous exudate.

Fig. 6 (case 26).—Section of the esophagus shown in figure 5, with ulceration, severe hyperemia and hemorrhage into the tissue.

pneumothorax on the right side. In addition there were hemorrhages in the left pleura, general venous congestion, pericarditis and right hydroureter. The esophagus appeared normal in its upper half. In the lower half it was dilated. The mucosa was dark purple and partly covered with a pale pink membrane. About 5 mm. above the cardia there was an opening on the right side which measured 2 mm. in diameter and led into the right pleural cavity. Microscopically, large areas of the mucosa were denuded of epithelium. Parts of the propria were necrotic and the debris was mixed with fibrin. Throughout all layers there was severe dilatation of the blood vessels, with areas of hemorrhage and leukocytic infiltration (fig. 6). The changes were severest near the point of perforation. Bacterial stains revealed a few gram-positive filaments and gram-positive and gram-negative cocci.

26. A 3 day boy: bronchopneumonia; esophagitis; dilatation of the heart; thrombi in pulmonary arteries and the right renal vein; hemorrhagic changes throughout the right kidney; focal fibrosis of the liver; acute splenitis; subdural hemorrhage.

27. A boy weighing 2,810 Gm. was born spontaneously at term after twelve hours of labor. His respiration was normal and his cry strong. On the following day he became cyanotic and was treated with oxygen. He was bringing up large quantities of mucus and blood. Four days after birth, respiration became labored, there was cyanosis and the baby died. Autopsy revealed: atresia of the esophagus with tracheoesophageal fistula; bronchopneumonia; esophagitis; tetralogy of Fallot; patent foramen ovale; defect of the radius. The lower portion of the esophagus originated from the trachea 1 cm. above the bifurcation. It connected with the stomach as usual. The mucosa was dark red and covered with sticky mucus. Microscopically, the epithelium was absent. The propria was partly necrotic and partly absent. There was marked leukocytic infiltration.

28. A 4 day girl: erythroblastosis (enlargement of the spleen with hemosiderosis, kernicterus); esophagitis; left hydroureter without occlusion; moderate dilatation of the heart.

29. A girl weighing 1,460 Gm. was born at home and admitted to the hospital eighteen hours later. Forty-two hours after birth she vomited mucus and large amounts of dark brown material. She was fed by gavage. The abdomen became distended, and the patient died six days after birth. Autopsy revealed ulcerative gastritis, peritonitis, esophagitis, bronchopneumonia and focal atelectasis. It was believed that peritonitis had developed by extension from the lesion in the stomach. The esophagus showed, just above the cardia, a circular area measuring 2 to 5 mm. in width, which was pale yellow and dull and had a dark red border. Microscopically, there was ulceration with necrosis of the propria and infiltration of polymorphonuclear leukocytes. In the submucosa and muscularis the veins were greatly congested and some were thrombosed (fig. 7).

30. A 6 day boy: prematurity; jaundice; kernicterus of brain and spinal cord; esophagitis; general edema; effusion in all serous cavities; fibrinous pleuritis; thrombi in pulmonary veins; hemosiderosis of the spleen. It was never established whether or not this infant had erythroblastosis.

31. An 8 day girl: prematurity; confluent bronchopneumonia with early abscess formation and fibrinous and fibrous obliteration of the right pleural cavity; esophagitis.

32. An 8 day boy: prematurity; bronchopneumonia; interstitial emphysema; subarachnoid hemorrhage; enteritis; esophagitis; jaundice; horseshoe kidney.

33. A 17 day boy: inflamed lumbosacral meningocele; hydrocephalus; microgyria; bronchitis; focal atelectasis; esophagitis.

34. A 17 day boy: gastritis; enteritis; organizing fecal peritonitis; esophagitis; enlargement of the spleen; jaundice; decubitus ulcer of the left buttock.

35. An 18 day girl: congenital idiopathic hypertrophy of the heart; dilatation of the heart; general edema; pulmonary congestion and edema; interstitial pneumonia; edema of the brain; esophagitis.

36. A 19 day girl: inflamed encephalocele; old hemorrhage in the left adrenal gland; focal atelectasis; esophagitis; follicular cysts of the ovaries.

37. A 22 day girl: prematurity; bronchopneuomnia; esophagitis; moderate subarachnoid hemorrhage; thrombosis of a renal vein; malnutrition.

38. A 1 month boy: moderate edema of the subcutaneous tissue; plegmonous inflammation of the neck region including the esophagus and the larynx; acute pancreatitis; partial pulmonary atelectasis.

39. A 6 week boy: syphilitic lesions of liver, adrenal glands, kidneys, intestine, thymus and femur; bronchopneumonia; esophagitis; ascites.

40. A 6 week girl: syphilitic periostitis; degeneration of the liver with questionable atresia of bile ducts; jaundice; polycystic kidneys; cystic fibrosis of the pancreas; bronchiectasis; bronchopneumonia; emphysema; esophagitis.

41. A 2 month girl: bronchopneumonia; hypertrophy and dilatation of the left ventricle of the heart; esophagitis; erosions of the stomach; follicular cysts of the ovaries.

42. A 2 month girl: interstitial pneumonia; esophagitis; congestion and swelling of the brain; hemorrhage in pleura and thymus; mild glomerulosclerosis; follicular cysts of the left ovary.

43. An infant girl was admitted at the age of 3 months with cough, hoarseness and fever. Her pharynx was red, and there was bronchial breathing and dulness over the upper lobe of the right lung. Two days later the right lung was completely dull to percussion. The infant received oxygen, penicillin and sulfadiazine and was fed by gavage. Two days later respiration became very rapid: there was bubbling at the mouth, as well as a bloody discharge from the nose. On the following day a transfusion of 50 cc. of blood was given, and one day after this the infant died. The Kahn test was strongly positive. At autopsy the body weighed 4,620 Gm. Syphilitic lesions were present in liver, kidneys, thymus and femur; other findings were: bronchopneumonia with abscess formation; enlargement of the spleen; edema; esophagitis; absence of the left kidney and ureter; uterus unicornis on the right side; bilateral coloboma of the iris. The mucosa of the esophagus was pale gray, opaque and glistening. Scattered throughout the length of the esophagus there were shallow, sharply outlined ulcers with a red base, measuring 2 to 3 mm. (fig. 8).

44. This was a premature girl with a birth weight of 1,600 Gm. She was admitted at the age of 3½ months with an infection of the upper respiratory tract, vomiting, diarrhea and severe malnutrition. Two days later she underwent a sudden rise of temperature and swelling of the abdomen. She was given clysis and was fed by gavage, but died. At autopsy the body weighed 2,465 Gm. The findings were: bronchopneumonia; focal atelectasis and emphysema; acute ulcerative enteritis; esophagitis; hypertrophy of the left ventricle of the heart; hydrocephalus of the left lateral ventricle; umbilical hernia. A perforation of the stomach and esophagus appeared to have occurred after death. The esophagus showed in addition to this perforation, in its lower portion, two areas in which the mucosa was dark red and bulging (fig. 9). Microscopically, these areas showed loss of the epithelium and were covered with thick layers of clotted blood (fig. 10).

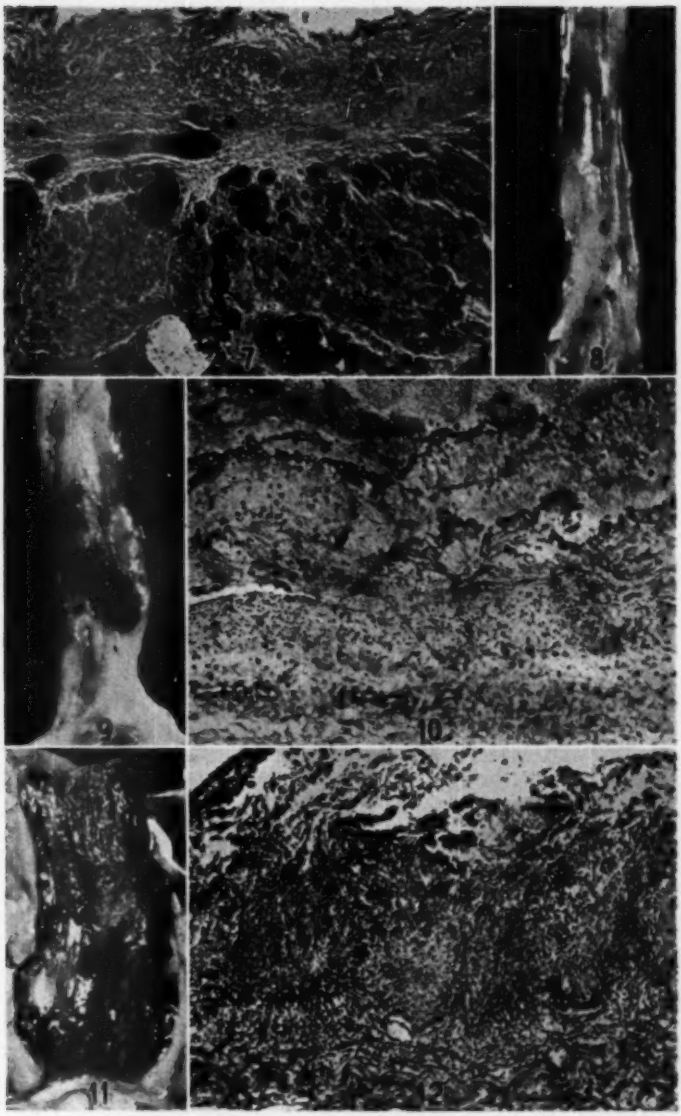


Fig. 7 (case 29).—Ulceration and infiltration of the mucosa, and severe hyperemia of the muscularis.

Fig. 8 (case 43).—Ulcers scattered along the entire esophagus.

Fig. 9 (case 44).—Ulcers covered with blood clots.

Fig. 10 (case 44).—Section of the area shown in figure 9. The upper half of the figure is clotted blood. The mucosa is absent. The lower half of the figure shows muscularis, mucosa and submucosa.

Fig. 11 (case 45).—Hemorrhagic esophagitis.

Fig. 12. (case 45).—Section of the esophagus shown in figure 11, with ulcers covered by a thick membrane. The latter consists of fibrin, erythrocytes, leukocytes and many threads of fungus.

The underlying tissue was extremely hyperemic and showed large areas of hemorrhage and a moderate leukocytic infiltration.

45. This premature girl had a birth weight of 1,460 Gm. At the age of 3 months she weighed 2,580 Gm. and began to have loose stools and vomit blood-tinged material. Shortly before death at 3½ months of age she vomited blood on several occasions. At autopsy the body weighed 2,540 Gm. Autopsy revealed: acute meningitis; cystic fibrosis of the pancreas; bronchiectasis; focal emphysema and atelectasis; bronchopneumonia; degeneration of liver and kidneys; jaundice; edema; ascites; bilateral pleural effusion; hemorrhage into the right renal medulla; esophagitis; enteritis. The mucosa of the esophagus was red and covered with dark brownish red material (fig. 11). Microscopically, the entire wall of the esophagus was covered with a thick membrane consisting mostly of fungus with a few leukocytes and cellular debris. Under this membrane there were ulcerations, some of which reached into the submucosa (fig. 12).

46. A 3½ month girl: bronchopneumonia; interstitial pneumonia; thrombi in pulmonary and renal veins; esophagitis; follicular cysts of the ovaries.

47. A 4 month girl: moderate enteritis; esophagitis; thrombosis of vessels of the occipital lobes of the brain with focal necrosis; follicular cysts of the ovaries.

48. This boy had a birth weight of 1,860 Gm. He was discharged weighing 2,300 Gm. and was again admitted at the age of 2 months, weighing 2,700 Gm. He vomited and had a rash. Since birth the stools had contained blood, the source of which was believed to be in rectal condylomas. The Kahn test was strongly positive. The patient died at the age of 4 months. At autopsy the body weighed 2,450 Gm. The observations included: esophagitis with hemorrhage; focal pulmonary atelectasis; fibrinous perisplenitis; syphilitic osteochondritis and periositis; fissures at the angles of the mouth. The lumen of the esophagus was filled with a dark red cast which had a dull surface and measured 1 by 1.5 by 4 cm. The lower portion of the esophagus was moderately dilated, and several areas were covered by pale, opaque membranes (fig. 13). Microscopically, there were areas in which the epithelium was absent and the surface was formed by necrotic tissue with pyknotic nuclei. These areas were severely infiltrated by polymorphonuclear leukocytes (fig. 14).

49. A 4 month girl who died after complete anuria lasting one week, following injection of an antisyphilitic drug: necrosis of proximal convoluted tubules of the kidney with regeneration; moderate cirrhosis of the liver; extreme general edema; bronchopneumonia; pulmonary edema and atelectasis; esophagitis; follicular cysts of the ovaries; vaccinia at the site of inoculation.

50. A 4½ month girl: focal acute meningitis; general edema; ascites; fatty liver; esophagitis; bronchitis; cholangitis; follicular cysts of the ovaries.

51. This infant was well until the age of 5 months, when he began to vomit all feedings. There was no diarrhea. He weighed 3,500 Gm., was severely malnourished and had on the body a maculopapular rash. A systolic murmur was heard over the apex of the heart. The patient died five days after admission. At autopsy the body weighed 3,100 Gm. The abnormalities included: a perforated duodenal ulcer; peritonitis; esophagitis; thickening of the aortic valve; petechial hemorrhages of the brain. At the cardia there was an ulcer measuring 3 by 4 mm. Microscopically, it had a narrow opening and a more extended deep portion which undermined the superficial layers. On one side of this ulcer there was an area which was densely infiltrated by round cells. No micro-organisms could be demonstrated in this section.

52. An 8 month boy: laryngotracheitis; esophagitis; chronic bronchitis; focal atelectasis; acute splenitis.

ANALYSIS OF ASSOCIATED FACTORS FOR ETIOLOGIC POSSIBILITIES

An attempt will be made to determine in the case of each clinical and pathologic finding associated with esophagitis whether it is a cause

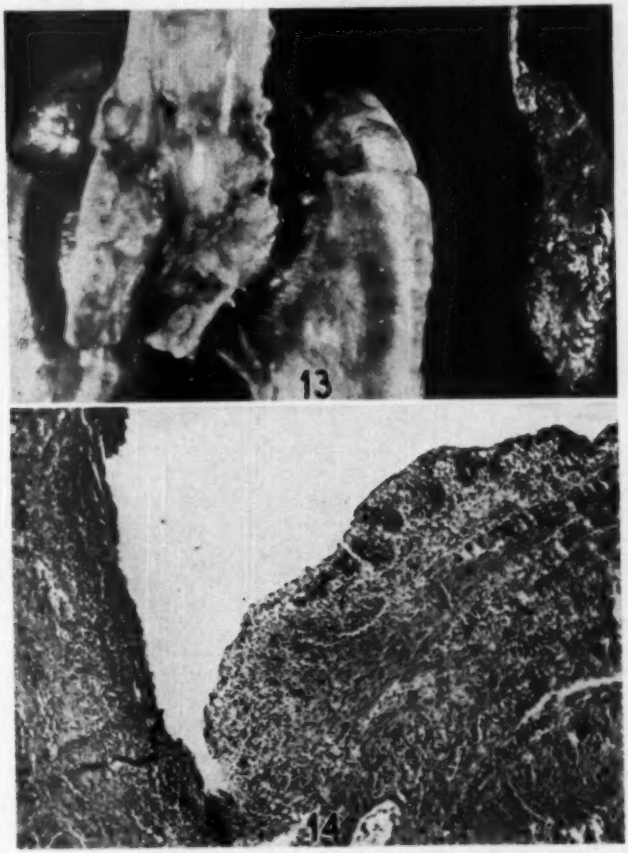



Fig. 13 (case 48).—Posterior view of the thoracic viscera. The esophagus is dilated and ulcerated. It contained a firm blood clot, shown to the right.

Fig. 14 (case 48).—The esophagus seen in figure 13 shows extensive ulceration (left side of figure).

or a sequel of the condition under consideration. This can obviously not be done with certainty in all instances. It is important to remember

that the cause and the significance of esophagitis are not necessarily the same in all cases.

If one considers the arbitrary age groups established in tables 1 and 2, it will be clear that the first group, i. e., infants of the first half month of life, differs in many respects from the others and deserves separate attention at several points of the following discussion.

*Obstetric Factors.*—There are several factors in the newborn group which might bear a causal relation to the clinicopathologic entity of esophagitis.

Prematurity: Of the 33 infants of the neonatal group, 13 are considered premature, weighing at birth less than 2,500 Gm. It is obvious that despite the large proportion of premature infants in this series this cannot be a significant factor in the induction of esophagitis, because a comparable series of neonatal infants dying without esophagitis contains a larger percentage of premature infants.

Difficult Labor: An abnormal maternofetal parturient relationship may play a role in the production of esophagitis. Of the 33 infants, 11 may be considered as having undergone a more spartan type of delivery than is desirable. There were 5 patients who were delivered with great difficulty: 1 with brow presentation, delivered by version and extraction; 1 with prolapse of the umbilical cord; 1 with the cord wound tightly around the neck, and 1 discharging meconium throughout labor. In view of the preponderance of infants delivered with relative ease it appears that difficult labor in itself does not play a prominent role in the causation of esophagitis. An interesting sidelight comes from the fact that two of the mothers with prolonged labor, a third with placenta previa, and an Rh-negative mother who was not in labor were delivered by cesarean section; thus the vaginal delivery was obviated in our search for causes of esophagitis.

Mechanical Trauma: What role could be assigned to the use of tracheal aspiration, gavage and Wangensteen suction? Seventeen babies had the trachea aspirated, 6 were fed by gavage, and 2 had a Wangensteen suction apparatus set up. Since the remaining babies were not mechanically traumatized, and since the pathologic condition was most severe at the cardiac rather than at the point of introduction of the instrument, mechanical factors seem to be eliminated as etiologic agents.

Neonatal Asphyxia: It is difficult to ascertain the role of asphyxia, principally because the clinical diagnosis is not always clear. Just how much anoxia is required, and for how long a time, in order to produce asphyxia in a newborn infant or in an infant in utero is not well known. Nineteen of 33 infants showed moderate to severe asphyxia as evidenced by cyanosis, respiratory difficulty and need for resuscitation or the administration of oxygen at birth. In view of the difficulties of judging the degree of asphyxia by examination of the living infant, it is of interest

to turn to pathologic evidence. It has been our experience that the usual signs of asphyxia, such as severe general venous congestion, hemorrhages in serous membranes or massive aspiration of the vernix caseosa, can be reliably ascertained only in infants less than 3 days of age. Of 20 infants with esophagitis, aged from 8 hours to 2½ days, 14 showed definite signs of asphyxia. The incidence of asphyxia may not be significantly higher in this group than in an unselected group; however, one gains the impression that a relatively large number of severely asphyxiated infants is found among those with esophagitis. It may be significant that necrosis of the walls of coronary arteries, which has recently been recognized as occurring in asphyxiated infants,[8] is common among patients with esophagitis. Of 14 liveborn infants found to have the vascular lesion, 5 had esophagitis. Laugier and Leblond[9] found ulcers in the gastrointestinal tracts of animals subjected to anoxia. An explanation of this effect of asphyxia may be the fact that shock is produced. This will be discussed later.

Summary of Obstetric Factors: Although no single factor appears to be the causative agent in the production of esophagitis in newborn infants, this group of patients does vary considerably from a comparable series of unselected newborn infants who die, in the following respects: 1. This group contains a larger number of full term infants. The same was found in a series of infants who had necrosis of the coronary arteries. In both groups (which overlap, as was mentioned before) this may be due to the fact that large infants are more prone to certain types of birth trauma in the widest sense of the word, including asphyxia. 2. Only 3 of 33 infants of the first half month of life can be said to have been born of a normal pregnancy of a normal mother, with normal labor and delivery. One thus gains the impression that obstetric complications and severe asphyxia predispose an infant to esophagitis.

*Shock.*—It is known that necrosis occurs in various parts of the body in shock, and ulceration of the gastrointestinal tract is one of the most characteristic forms of lesions due to shock.[10] Esophageal ulcers have been found by Penner and Bernheim[11] to occur in adults in shock; they resemble structurally those reported here. The same authors cited from old literature data concerning esophagitis of infants, but they did not explicitly link these with shock. In view of the absence of any indications of an infectious cause of esophagitis of infants (see later comment) it is proper to consider shock as a possible cause. In the histories of our patients there is usually no mention of shock; however, one must

8. Gruenwald, P.: Am. Heart J., to be published.

9. Laugier, H., and Leblond, C. P.: Rev. canad. de biol. **2**:474, 1943.

10. Klemperer, P.; Penner, A., and Bernheim, A. I.: Am. J. Digest. Dis. **7**: 410, 1940.

11. Penner, A., and Bernheim, A. I.: Arch. Path. **28**:129, 1939.

remember that with infants, particularly during the neonatal period, the usual symptoms of shock cannot be relied on, and laboratory data are insufficient. In the largest group of our patients, namely the youngest ones, there is a high incidence of severe asphyxia, as revealed by clinical data as well as pathologic observations; this was described in the preceding section. Anoxia is an important cause of shock, as has been discussed in detail by Moon.[12] Holt and McIntosh [13] stated that the second degree of asphyxia of the newborn is comparable to surgical shock. In addition to asphyxia, severe dehydration of infants, which is known to result in hemoconcentration, will result in shock. It is therefore possible that not only local damage of tissue but also shock operates in producing esophagitis in asphyxiated newborn infants, provided that they survive sufficiently long. The localization in the lower portion of the esophagus may be due to local peculiarities of the circulation during infancy much as peculiarities of different species determine the localization of shock lesions in animals.[10] The gastric erosions occurring in some of our cases, and a duodenal ulcer in one instance, may also be explained on the basis of shock. The fact that lesions of the stomach show less reaction may be due to a reduced chance of secondary infection. Wyatt and Khoo [14] also found less leukocytic infiltration in gastric ulcers than in those elsewhere in the digestive tract.

*Lesions of the Brain.*—Since the work of Cushing [15] it has been established that ulcers of the gastrointestinal tract occurs frequently in persons with various pathologic changes in the brain. Cushing reported that in the Children's Hospital in Boston there were during one year 4 patients with lesions of the brain examined at autopsy in whom an ulcer had perforated the esophagus.

The subject has recently been discussed by Wyatt and Khoo,[14] who found that theories explaining ulcerations in connection with brain lesions or shock do not differ fundamentally. Among 199 infants who died in the first half month of life and were examined during the period of our investigation there were 33, or 16.6 per cent, with esophagitis. Within this group there were 66 with intracerebral hemorrhage, and among these 11, or 16.7 per cent, had esophagitis. Mechanical injury of cerebral tissues at birth is therefore not an apparent cause of esophagitis. Esophagitis is, however, definitely correlated with another type of brain lesion: 5 of 6 infants who had kernicterus and who were examined by us at autopsy had esophagitis. This observation is not

12. Moon, V. H.: Shock: Its Dynamics, Occurrence and Management, Philadelphia, Lea & Febiger, 1942.

13. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, 1939.

14. Wyatt, J. P., and Khoo, P. N.: Arch. Path. **47**:110, 1949.

15. Cushing, H.: Surg., Gynec. & Obst. **55**:1, 1932.

isolated. We are indebted to Dr. L. Strauss for information to the effect that among 7 infants with kernicterus examined at autopsy at the Mount Sinai Hospital in New York during the past few years, 4 were found to have esophagitis, even though it was not especially looked for. Pfältzer [16] suggested long before the cause of erythroblastosis was known that kernicterus was an infectious disease with the portal of entry in the esophagus, because the 2 patients whom he examined both had esophagitis.

*Infection.*—In the majority of our cases bacterial stains were done on sections of the esophagus in order to demonstrate both gram-positive and gram-negative micro-organisms. The following results were obtained.

| | |
|---|---|
| No micro-organisms | 21 |
| Bacteria only | 15 |
| Fungi (usually associated with bacteria) | 6 |
| | 42 |

The number of cases showing no organisms is not significant to the full extent, as some patients were treated with antibacterial agents. Yet it is probable that no significant growth of micro-organisms took place in the esophageal lesions of some of these infants. More definitely significant is the lack of uniformity of the flora demonstrated in tissue sections. Gram-positive or gram-negative cocci or rods of various shapes were seen in various arrangements, sometimes associated with fungi. This suggests a secondary infection rather than a primary infectious cause of the inflammatory and ulcerative changes. The same type of infection is known to occur in lesions due to shock.[10] Other investigators [17] have reported a higher incidence of fungous infection in their cases of esophagitis in infancy. This may well be due to the fact that we have included relatively inconspicuous cases of esophagitis, in which the lesion may be less likely to contain fungi, and also to the fact that the number of very young infants in our series is large.

Esophagitis was occasionally found associated with infectious disease occurring in close proximity or elsewhere in the gastrointestinal tract (table 2), but such an association was not sufficiently constant to serve as a basis for the explanation of the cause of esophagitis except, perhaps, in a few cases.

The possible significance of secondary infection of esophageal lesions for the further course of the patient will be discussed later.

*Malformations.*—There are numerous reports in the literature—for example, that of Wyllie and Field [18]—indicating that ulcers, apparently

16. Pfältzer, B.: Ztschr. f. Geburtsh. u. Gynäk. **76**:683, 1915.
17. Ebbs,[5] Reye.[6]
18. Wyllie, W. G., and Field, C. E.: Arch. Dis. Childhood **21**:218, 1946.

of peptic nature, occur in the so-called congenitally short esophagus, that is, in cases in which a portion of the stomach is above the diaphragm and apparently communicates more freely with the esophagus than usual. We have not seen cases of this kind. The only instance of a malformation in our series was one of atresia of the esophagus with tracheoesophageal fistula (case 27). This occurrence does not appear to be significant, since the majority of infants born with the same malformation do not have esophagitis.

*Regurgitation of Gastric Juice.*—The predilection of esophagitis for the lower portion of the organ, the termination at the border of gastric mucosa and the frequent dilatation of the esophagus and probably the cardia are all suggestive of an action of gastric juice in the production of esophagitis. Vomiting is on record in a high percentage of cases (table 2). Some of these factors may be either the cause or the sequel of esophagitis, and it is therefore impossible to decide what role the regurgitation of gastric juice plays in the causation of the lesions. Mallory and Weiss [19] suggested that a disturbed mechanism of vomiting may cause lacerations just above or below the cardia. This is one of several questions which may be answered when the occurrence of esophagitis becomes better known, and clinical observations become available. Along with regurgitation one should also keep in mind the possibility of delayed passing of food through the cardia.

*Miscellaneous Factors.*—In 1 instance (case 49) uremia may have been responsible for the ulceration.

Direct extension of an infectious process accounts for a small number of instances of esophagitis, namely, from a phlegmonous inflammation of the entire neck area in case 38, from a membranous laryngotracheitis in case 52 and from severe, ulcerative gastritis in case 29.

### COMMENT

If one compares the possible causal factors in the neonatal group and in the other patients, it appears that a semblance of uniformity of the history and associated findings is present only in the former. This may well be accounted for by the fact that the trauma of birth is common to all newborn infants and overshadows all other factors. In later life there is a much greater variety of extrinsic influences, which are therefore more difficult to evaluate. This holds particularly for the factors which may produce shock.

One is not justified in assuming a priori that all instances of infantile esophagitis are due to the same cause. Among the possible causes discussed, shock is of particular interest because of its significance for the

19. Mallory, G. K., and Weiss, S.: Am. J. M. Sc. **178**:506, 1929.

entire organism, and the possibility of treating it once it is recognized.[20] This should not, however, make one fail to seek for other causative factors.

### CLINICAL SIGNIFICANCE OF ESOPHAGITIS

It is obvious that the severity of esophagitis, as well as its significance in the individual case, varies in wide limits. There can be no doubt that in some of the cases esophagitis was an accidental finding, unrelated to the course of the principal disease and to the death of the patient. In others the fatal outcome was principally or partially due to the lesions of the esophagus; excellent examples are the 2 cases in which the pathologic process perforated into a pleural cavity. It seems definitely worth while to make the diagnosis of esophagitis in all those cases in which any signs or symptoms may be detected; this would probably not include the mildest cases, which are of little significance.

Vomiting is often associated with esophagitis. Whether it produces the lesion, and the gastric juice is an irritant factor producing the initial damage to the mucosa, or whether esophagitis initiates the vomiting, there is likelihood that vomiting will occur in esophagitis, as seen in 34 cases of our series. In 17 of these cases the vomitus contained blood; in 1 the hemorrhage was profuse, and in another case the esophagus contained at autopsy a large cast of clotted blood. In fact, the diagnosis of esophagitis is strongly suggested when a baby vomits blood, the more so when there is no abnormal bleeding tendency demonstrable by hematologic studies. We are not aware of any other lesion giving rise to hematemesis which occurs in infants with nearly as great a frequency as esophagitis. In 3 cases blood made its appearance in the stool in sufficient amounts to be grossly visible without particular attention to this sign. It is probable that close examination, including a chemical test, would reveal a much higher incidence of melena. Many instances of melena neonatorum are probably due to esophagitis and should be tentatively evaluated as such.

In addition to hemorrhage and perforation, significant sequelae may arise from infection. It has been mentioned that infection of esophageal ulcers is probably secondary to the true cause. The possibility must be thought of that bacteria may find their way from these ulcers to other parts of the body, as from foci of infection elsewhere.

Esophagitis should be diagnosed not only for its own sake. It is a useful diagnostic sign and should lead the pediatrician to seek further evidence of shock. One may then initiate early therapy, not so much of the local lesion as of the underlying general condition. This is of particular importance because the diagnosis of shock is probably often

20. A study of a variety of pathologic conditions observed in asphyxiated newborn infants suggesting that they are in shock is in progress.

missed in infants. Whether or not treatment of esophagitis itself is desirable and feasible will become apparent only when more experience with clinically recognized cases is at hand.

In this connection a recent experience, conditioned by the present finding, may be mentioned. A 4 day old infant was brought to our attention because it had vomited blood. The diagnosis of esophagitis was entertained, and the infant was examined for indications of shock. The patient was severely dehydrated and breathed poorly, and the extremities were cold. The pulse was irregular and small. The blood pressure was too low to be determined. A jugular vein was entered in an attempt to obtain blood for a hematocrit test, but only one drop of blood could be obtained. The concentration of hemoglobin was in excess of 24 Gm. per hundred cubic centimeters; the number of erythrocytes was higher than 8,000,000 per cubic millimeter. It is apparent that this infant exhibited many of the signs of shock. It died on the same day. Autopsy revealed severe esophagitis, gastric erosions, pneumonia, focal pulmonary atelectasis and fatty and albuminous degeneration of the liver. It remains to be seen how infants with similar conditions will react to therapy for shock.

## SUMMARY

Acute esophagitis, usually with ulceration, was found in 1 out of every 6 infants in a series of 310 autopsies. It is believed that the significance of this lesion for the patient's course ranges from an unimportant accidental finding to the principal cause of death.

Various possible causes are considered, and no single factor is found which might explain all cases. It is suggested that in many of the present cases esophagitis was a "shock lesion." In the neonatal group of patients, shock may have been the result of various types of birth trauma, including asphyxia.

Micro-organisms were demonstrated in tissue sections in half the cases. They were of different types and are believed to have been secondary invaders. Esophagitis can thus conceivably be a focus from which infection may spread.

Vomiting and hemorrhage occurred frequently in the patients with esophagitis; perforation into the right pleural cavity was encountered twice.

An effort should be made to diagnose esophagitis in living patients, not only because the lesion, if severe, should be treated, but because it may be an indication of shock, which is difficult to recognize in infants.

The validity of the present suggestions will be ascertained, and the significance of esophagitis properly evaluated, only when more clinical observations are available.

# PATHOLOGY OF EXPERIMENTAL IMMERSION FOOT

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THIS report deals with the data obtained in the last of a series of studies on the local effects of exposure to cold in man and in experimental animals. Previous investigations [1] established that the injuries resulting from local freezing and from chilling in man had a common cause, namely, vascular occlusion. Subsequent study [2] revealed that the lesions produced in the legs of rabbits by freezing could be similarly explained. In the present investigation we attempted to determine whether the mechanism of injury by chilling in rabbits resembled that of damage by freezing.

## METHODS

Twenty-eight rabbits were studied anatomically. The method of exposure was discussed in detail in a previous report.[3] One hindleg of each of 22 rabbits was kept in circulating water at a temperature of 35 to 39 F. for three or four days. Half of the animals died or were killed immediately after the period of exposure; the remainder died or were killed at intervals of from four to one hundred and thirty-five days after exposure. One hindleg of each of 3 additional rabbits was fixed in an empty cylinder while the animals stayed in the same apparatus; and, similarly, the legs of 3 other control animals remained in cylinders filled with water at room temperature.

The exposed leg and the opposite unexposed extremity of each rabbit were fixed in a 4 per cent solution of formaldehyde. A number of pieces were taken

From the Armed Forces Institute of Pathology, Washington, D. C. (Dr. Friedman [present address: Cedars of Lebanon Hospital, Los Angeles]) and the New York Medical College (Metropolitan Hospital) Research Unit, New York (Drs. Lange and Weiner).

1. Friedman, N. B.: Am. J. Path. **21**:387-433, 1945; Am. J. Clin. Path. **16**:634-639, 1946. Friedman, N. B., and Kritzler, R. A.: Am. J. Path. **23**: 173-187, 1947.

2. Friedman, N. B.; Lange, K., and Weiner, D.: Am. J. Med. Sc. **213**:61-67, 1947

3. Lange, K.; Weiner, D., and Boyd, L. J.: Am. Heart J. **35**:238-247, 1948.

from the anterior and posterior groups of muscles within the exposed zone and above the line of exposure. The posterior tibial nerve was dissected free from the ankle to the knee, and segments at several levels were removed for study.

The tissues were dehydrated through alcohols, embedded in paraffin and stained with hematoxylin and eosin and by the Masson trichrome and Bodian methods. Frozen sections of nerve were stained for fat (with the sudan IV stain) and for myelin (by the Spielmeyer method).

## RESULTS

The functional alterations in these animals were discussed in detail in a previous paper [6] and the discussion will not be repeated here. The present report deals mainly with histopathologic changes.

Neither vascular lesions of the frostbite type nor ischemic gangrene was seen. The occasional complicating cellulitis with necrosis could clearly be ascribed to secondary infection of a traumatized part. There were no significant changes in the skin or the subcutaneous tissue.

*Changes in Muscles.*—Acute lesions (figs. 1, 2 and 3) were noted immediately after exposure. Coagulation of the cytoplasm of the muscle fibers had led to replacement of the normal fibrillar substance with hyaline masses, ribbons and clumps of granular material. Sometimes edema fluid distended the sarcolemmal sheath about the cytoplasmic fragments, and the sarcolemmal nuclei had undergone proliferation. The alterations in the fibers were often patchily distributed and occasionally involved only segments. There were also interstitial edema and a moderate infiltration of cells, including leukocytes and lymphocytes.

In animals killed at varying intervals after exposure more chronic changes (figs. 5 and 7) were evident. The sarcolemmal nuclei of the distorted and atrophic fibers had proliferated, and many bizarre forms were encountered; there was considerable interstitial fibrosis. Nevertheless, the muscles of some animals killed approximately four months after exposure were essentially normal.

Occasionally parasitic infection caused focal degenerative myositis in both the exposed and the control legs. In 2 instances degenerative changes similar to those attributed to cold were also noted in muscle from an unexposed region. Sometimes the damage in the exposed leg was so sharply restricted that muscle adjacent to an injured area was virtually uninvolved.

*Changes in Nerves.*—In animals killed immediately after exposure there were no significant alterations in the nerves. However, five days after exposure degenerative changes appeared and persisted for from one to five weeks. The lesions consisted essentially of demyelination (fig. 9) and degeneration of axis-cylinders. The myelin was broken up into segments and balls, and free fat was evident, especially in

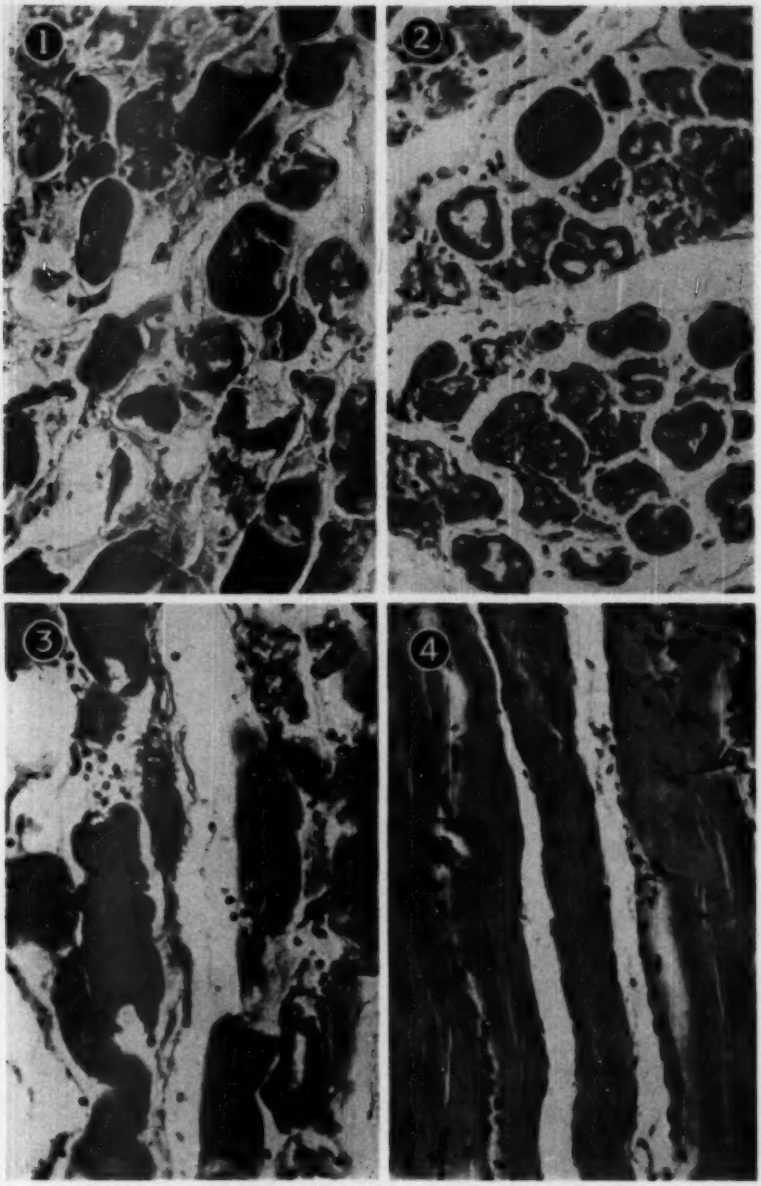


Fig. 1 (A. F. I. P. Neg. 103108).—Degeneration of muscle fibers after forty-eight hours' exposure to cold; hematoxylin and eosin; × 185.

Fig. 2 (A. F. I. P. Neg. 103106).—Degeneration of muscle fibers and cellular reaction after ninety-six hours' exposure; hematoxylin and eosin; × 185.

Fig. 3 (A. F. I. P. Neg. 103089).—Degeneration of muscle fibers and cellular reaction after one hundred and twenty hours' exposure; hematoxylin and eosin; × 185.

Fig. 4 (A. F. I. P. Neg. 103088).—Normal muscle from unexposed leg of same rabbit as in figure 3; hematoxylin and eosin; × 185.

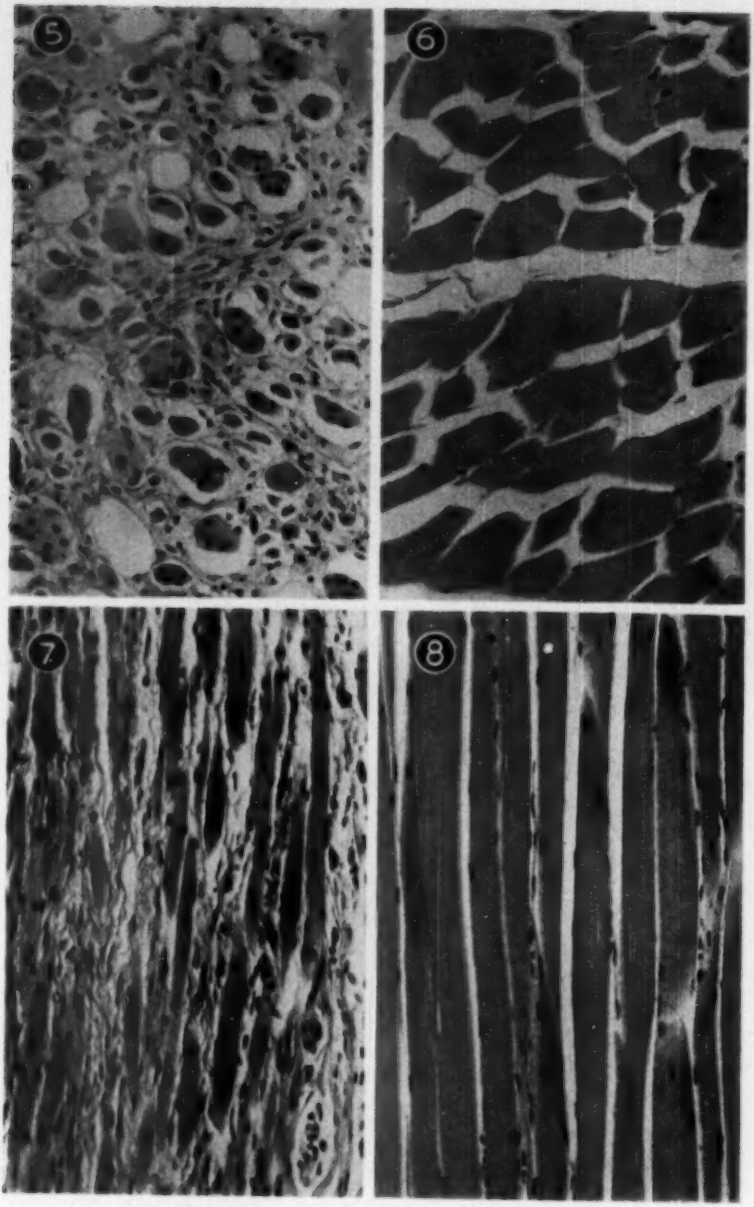


Fig. 5 (A. F. I. P. Neg. 103110).—Atrophic muscle showing multinucleated fibers and interstitial fibrosis twenty days after ninety-six hours' exposure; hematoxylin and eosin; × 185.

Fig. 6 (A. F. I. P. Neg. 103109).—Normal muscle from unexposed leg of same rabbit as in figure 5; hematoxylin and eosin; × 185.

Fig. 7 (A. F. I. P. Neg. 103095).—Atrophy of muscle and interstitial fibrosis thirty-three days after seventy-two hours' exposure; hematoxylin and eosin; × 185.

Fig. 8 (A. F. I. P. Neg. 103096).—Normal muscle from unexposed leg of same rabbit as in figure 8; hematoxylin and eosin; × 185.

phagocytic cells. Staining of axis-cylinders showed fraying and vacuolation. Regeneration of fibers began about one month after exposure, and at the end of four months the nerve fibers appeared practically normal. Regeneration of the fibers was especially conspicuous in rabbits which had exhibited functional recovery. The increase in the number of neurilemmal nuclei persisted into the regenerating phase. Some proliferation of the mesenchymal cells in the endoneurial and perineural connective tissues was observed.

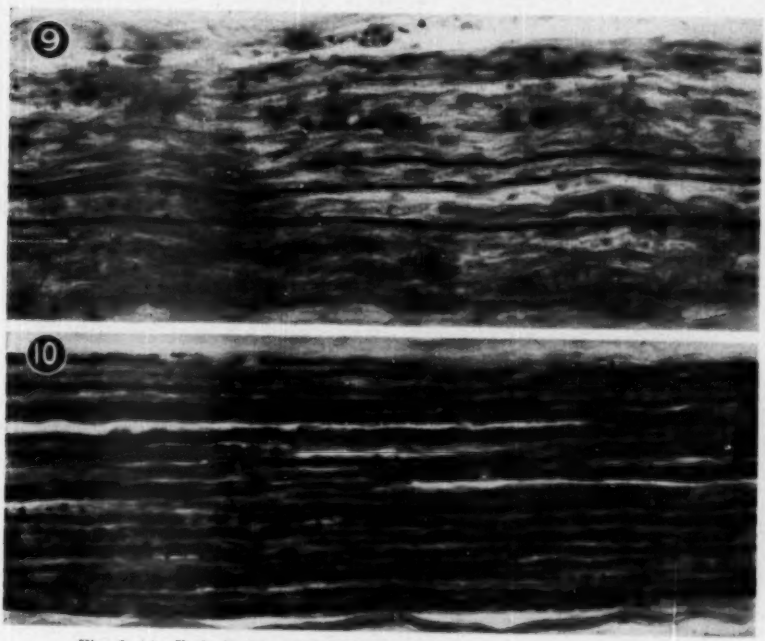


Fig. 9 (A. F. I. P. Neg. 103176).—Demyelination of nerve thirty days after ninety-six hours' exposure; myelin stain; × 235.

Fig. 10 (A. F. I. P. 103185).—Normal nerve from unexposed leg of same rabbit as in figure 9; myelin stain; × 235.

## COMMENT

The histologic changes suggest that cold directly affects muscle and nerve. The physiologic correlates of the anatomic changes have been discussed elsewhere.[3] There is no reason to consider either the neural or the muscular injury as primary; both probably were simultaneously incurred.

Two interpretations of the mechanism of damage suggest themselves. Cold may have a direct toxic action on cells, or secondary anoxia may be caused by circulatory disturbances. Since evidence of vascular occlusion was not observed, such anoxia would have to be postulated as resulting either from interference with the dissociation of oxyhemoglobin at low temperatures or from peripheral shunting of blood, through arteriovenous anastomoses, for example. The possibility of vascular spasm cannot be excluded. It is obvious that studies of the direct effects of cold on the physical and chemical properties of muscle fibers and particularly on their constituent structural proteins are in order.

The results of this study do not support the previously advanced concept that all injuries resulting from exposure to cold, whether by freezing or by chilling, have a common cause, namely, vascular occlusion. Instead, they are in harmony with the views of Blackwood and Russell,[4] who expressed the belief that the mechanisms of injury by freezing and by chilling are not identical. It is possible that the reactions of man to exposure to cold differ from those of rabbits.[5]

SUMMARY

Exposure of the hindlegs of rabbits to water at a temperature of 35 to 39 F. resulted in striking degenerative changes in muscle and nerve which appeared to be direct effects of cold. Vascular lesions such as are produced by exposure at temperatures below 32 F. were not observed. These results support the view that in rabbits, if not in man, there are essential differences between the injuries produced by freezing and those produced by chilling.

4. Blackwood, W., and Russell, H.: Edinburgh M. J. **52**:160-165, 1945.
5. Kreyberg, L.: Acta path. et microbiol. Scandinav. **26**:296-308, 1949.

# HEALING INCOMPLETE SPONTANEOUS RUPTURE OF THE AORTA

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THE AORTA is a remarkable blood vessel, withstanding continuous forceful pulsations from about the fourth month of intrauterine life until the complete cessation of cardiac activity. Its musculoelastic structure permits extreme variations of the force sustained, and the vessel compensates readily for these sudden changes. Oppenheim [1] found that pressures of more than 3,000 mm. of mercury were necessary to rupture a normal intact aorta; Robertson and Smith [2] found that over 600 mm. of pressure was necessary to produce artificial dissection of the media in portions of normal aorta. They also noted that the pressure required to cause dissection of the normal media was far greater than that observed in the most severe hypertension.

Rupture of the normal aorta is seen following certain types of trauma (blows from blunt forces, rapid deceleration) [3] and, less frequently, may occur spontaneously. Although Kaufman [4] stated that "even an apparently quite perfect aorta tears," the criteria published by the New York Heart Association insist that spontaneous rupture never occurs in a normal vessel, though recognizing that there may be an absence of extrinsic pathologic processes.[5] Congenital malformations, such as coarctation or hypoplasia, may predispose to rupture. A syphilitic aorta never ruptures unless the pathologic process has given rise to an aneurysm.

Spontaneous rupture of the aorta has not been frequently reported in the literature. Incomplete rupture which has gone on to partial or

From the Pathology and Medical Services of the United States Marine Hospital.

1. Oppenheim, F.: München. med. Wchnschr. **65**:1234, 1918, cited by Tannenbaum and Ferguson.[3]

2. Robertson, J. S., and Smith, K. V.: J. Path. & Bact. **60**:43, 1948.

3. Tannenbaum, I., and Ferguson, J. A.: Arch. Path. **45**:503, 1948.

4. Kaufman, E.: Lehrbuch der pathologischen Anatomie (translation by Reimann), Philadelphia, P. Blakiston's Son & Company, 1929.

5. de la Chapelle, C. E.: Nomenclature and Criteria for the Diagnosis of Diseases of the Heart, ed. 4, New York, New York Heart Association, 1945.

complete healing has been reported even less frequently. This has been described as incomplete rupture without dissecting aneurysm.[6] The following case is believed to be of interest since it illustrates healing spontaneous rupture as an unexpected autopsy finding.

## REPORT OF A CASE

A 56 year old Negro man was first treated for vascular hypertension at the United States Marine Hospital in January 1948. He returned in March 1948 with complaints of pressure in the left side of his chest, and dyspnea, which was greater at night and on exertion. There was no edema or cough.

The past history revealed that the patient had traumatized his left leg in 1936, for which he had a midthigh amputation and was subsequently hospitalized for four years. He had a penile lesion in 1925, but no history of treatment could be obtained. Serologic tests for syphilis were negative at this admission.

Physical examination revealed a moderately dyspneic and orthopneic Negro man. The lungs were clear, and the heart was enlarged to the left. The cardiac rhythm was regular, and the blood pressure was 240 systolic and 150 diastolic. The liver was palpable approximately 4 cm. below the right costal margin. The left inferior extremity was amputated at the midthigh, and slight edema of the right leg was noted.

Albumin (2 plus) and granular casts were in the urine; the albuminuria continued throughout hospitalization. Roentgenograms of the chest showed some enlargement of the heart, particularly of the left side, and lung shadows indicative of chronic passive congestion. This increased on subsequent roentgenograms.

The patient responded somewhat to treatment for cardiac decompensation, although he continued to have considerable nocturnal dyspnea and precordial pain, which was relieved with morphine and glyceryl trinitrate. Mercurial diuretics reduced his peripheral edema, but the periods of improvement were followed by regression. Gradually, increasing ascites and peripheral edema developed despite supportive treatment. Abdominal paracentesis yielded large volumes of serous fluid, which had an average total protein content of 3 Gm. per hundred cubic centimeters. The serum albumin gradually declined. The blood pressure remained at about 190 systolic and 110 diastolic.

In October 1948 auricular fibrillation was noted, and one month later an irregular spiking temperature of 101 to 103 F. began. The course was gradually downhill and the patient died in acute respiratory distress, nine and one-half months after his last admission.

*Autopsy.*—The body was that of an emaciated 56 year old Negro man. The abdomen was distended. Edema of the arms and right leg was present.

The heart weighed 550 Gm. The epicardium was roughened by a generalized granular exudate which was more pronounced in the region of the base of the heart. The myocardium was somewhat pale and softer than normal. The wall of the left ventricle measured 11 mm. in thickness, and the right ventricle, 3 mm.

Approximately 2.5 cm. above the sinus of Valsalva was a transverse rupture of the intima of the aorta (fig. 1), which extended around the circumference of the vessel. There was dissection of the intima and media for a distance of 2 cm. in each direction from the rupture. The entire lesion appeared to be covered by an endothelial surface, and three or four dense fibrous strands were present between the intima and the media. The adventitial surface was unchanged.

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6. Wenger, F.: Arch. Path. **36**:253, 1943.

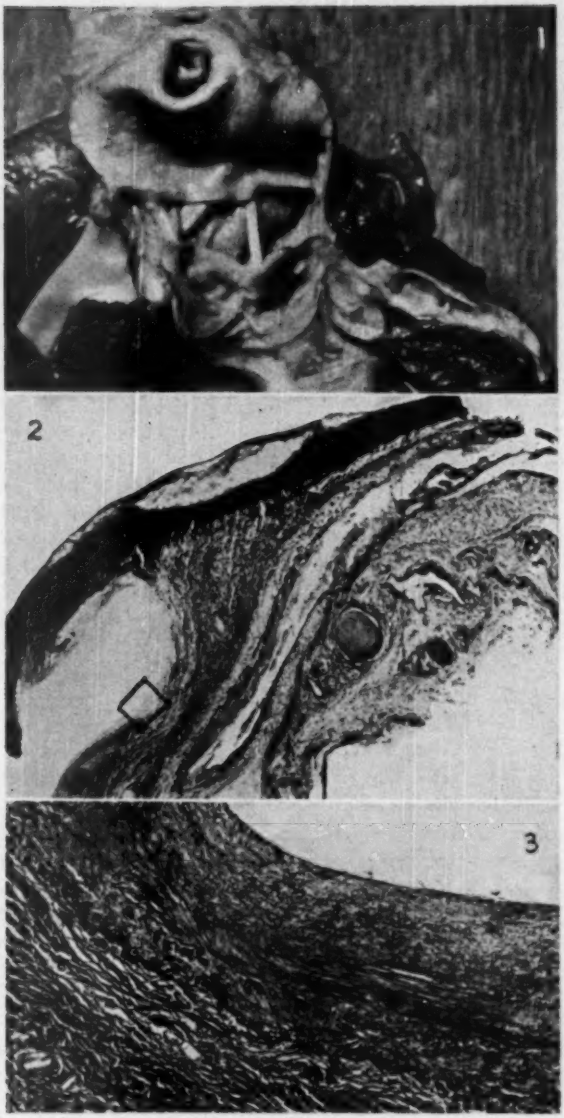


Fig. 1.—Photograph of the heart and aorta, showing the rupture of the aorta.
Fig. 2.—Longitudinal section through the site of rupture; elastic tissue stain; about × 10 (microtessar).
Fig. 3.—Intimal proliferation and disruption of the elastic fibers of the media; elastic tissue stain; × 100. This is a magnification of the area indicated in figure 2.

Other findings included confluent bronchopneumonia of both lungs and an organized thrombus at the bifurcation of the abdominal aorta, which partially occluded the left iliac artery.

*Microscopic Examination.*—Sections taken through the torn portion of the aorta showed an interruption of the intima (fig. 2) with an invagination of the musculoelastic folds. An upper free flap was present for a short distance. A proliferation of scar tissue, obliterating the normal structure, was present at the edges, and an attempt at healing was noted. The intimal cushion appeared slightly thickened in some areas. The structure of the vessel was better studied in an elastic-stained preparation (fig. 3), in which the remaining intact media could be demonstrated by the course of the elastic fibers. An endothelial layer covered the interrupted portions and was continuous with the intact margins of the aorta above and below the rupture. Occasional chronic inflammatory cells were seen in the thickened adventitial layer near the small blood vessels, but no cystic or necrotic changes were observed. A small atheromatous intimal plaque was present just proximal to the site of rupture but was not involved by it.

## COMMENT

The lesion encountered in this case was in the classic site, in the root of the aorta. The rupture was incomplete, involving only the intima and the media; an attempt at healing was demonstrated by the failure to dissect the endothelial covering and the fibrous strands between the free edges of the layers of aorta. Peery [7] discussed this entity, clinically and pathologically, in a most interesting paper which is subtitled: "A Heretofore Unrecognized Stage of Dissecting Aneurysm and a Cause of Cardiac Pain and Cardiac Murmurs." He stated that the lesion is rarely seen at autopsy and may easily be missed if the aorta is cut off shortly above the valve ring at necropsy. In recent lesions the edges were so sharp, straight and clearcut that an artefact was suspected at first. Indeed, in the present case the first impression was that a tear had been accidentally produced on opening the aortic ring. However, closer scrutiny showed this was not the case.

Reports of spontaneous rupture of the aorta without dissecting aneurysm are not frequently seen in the American literature. According to Peery,[7] this is because the lesion is frequently overlooked at autopsy. In 1942 he had collected 11 cases since 1935, and stated that this lesion occurred more frequently in his series than rupture of the aortic valve cusp if endocarditis was excluded. Strassman [8] reported that 24 cases of spontaneous rupture of the aorta were encountered in his series of 7,000 autopsies between 1936 and 1942.

Most commonly the lesion occurs just above the aortic valve ring, in the root of the aorta. It is transverse more often than longitudinal and may follow the circumference of the aorta for a variable distance.

7. Peery, T. M.: Arch. Int. Med. **70**:689, 1942.
8. Strassman, G.: Am. Heart J. **33**:508, 1947.

The changes subsequent to rupture are: healing to a variable extent; dissection or longitudinal extension of the proximal edge of the tear into the aortic valve. This tear is within the pericardial portion of the aorta; it produces insufficiency of the aortic valve and often produces hemopericardium and tamponade. If dissection occurs, death may rarely be avoided by formation of a second communication and a double tube effect. Healing of the rupture may take place if the patient is at complete rest, if dissection does not occur and if the tear is well above the aortic commissures.

Many factors have been suggested in attempts to explain this phenomenon. The persistence of the site of rupture has been supposedly justified by statements that there is "congenital weakness of the aorta at this place" [9] and that the "fixed portions of the aorta are most prone to rupture" (relative fixation occurring where the great vessels are given off).[10] Robertson and Smith,[2] however, found that the zone of greatest resistance to dissection was in the ascending segment. Kaufman [4] felt that it might be due to the pull exerted by the point of insertion of the aortic valves.

Concerning the pathogenesis of the lesion, there is further controversy. The greatest consideration has been given to medionecrosis cystica idiopathica as an etiologic factor in this local area of weakness. Yettra and Lasky [11] expressed the belief that this lesion is a congenital defect of the media of the aorta; they have noted it in conjunction with other congenital defects (arachnodactyly and patent foramen ovale). Rottino and Poppiti [12] remarked that in cystic medial necrosis the intima may be markedly wrinkled—almost resembling syphilitic aortitis. However, no mesaortitis is present. In severe medial degeneration there is compensatory thickening of the adventitia and connective tissue may fill in the place of rupture. Not uncommonly lymphocytes and plasma cells are encountered in the bases of recent tears. Their presence is believed to be part of the healing process rather than a specific inflammatory change.[7] In some cases, such as the present one, neither gross nor microscopic evidence of cystic degeneration can be demonstrated. Dominguez [13] feels that there was in all probability a focal area of medial necrosis which can no longer be demonstrated after the rupture has taken place.

Severe vascular hypertension of long duration has also been mentioned as a cause, and Peery [5] expressed the opinion that it is more

9. Abbott, M. E., cited by Tannenbaum and Ferguson.[8]

10. Rindfleisch, E.: Virchows Arch. f. path. Anat. **131**:374, 1873, cited by Tannenbaum and Ferguson.[8]

11. Yettra, M., and Lasky, I. I.: Am. Heart J. **33**:516, 1947.

12. Rottino, A., and Poppiti, R.: Arch. Path. **36**:201, 1943.

13. Dominguez, R.: Personal communication to the authors.

important than medial necrosis. He also surmised that local mechanical factors are at work in an area of local predisposition. The valve commissures exert a rocking force and pull on the aortic wall as they are driven shut in diastole. In persons with hypertension, straining or exertion, and fixation of the diaphragm with consequent increased intrathoracic tension, are given recognition.

Death may occur rapidly if hemopericardium and tamponade are produced, or more slowly in congestive failure secondary to aortic regurgitation.

SUMMARY

A case of healing incomplete spontaneous rupture of the aorta is presented. The patient was a 56 year old Negro man who had vascular hypertension and who died in congestive heart failure. The literature is briefly reviewed with regard to the etiologic factors and the pathogenesis.

# CENTRAL NECROSIS OF THE LIVER

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THE LIVER cells disappear from the central portion of the liver lobule in a variety of diseases. This may or may not be accompanied by clinical manifestations of liver insufficiency. As a rule, the extent of this hepatic alteration cannot be related to the clinical history. It appeared, therefore, indicated to reevaluate the etiologic factors and clinical significance of this rather common lesion which is called central necrosis. As an etiologic factor in addition to various injurious substances, passive congestion must be considered. From an understanding of the etiologic basis and significance of central necrosis of the liver, information may be obtained as to the pathogenesis of primary disease of the liver and of that secondary to infections, intoxications and passive congestion.

The older literature is primarily concerned with an exact morphologic description of central hepatic necrosis such as those given by Mallory and others.[1] The former found it 95 times in 1,190 autopsies, chiefly in acute infectious diseases; in 45 cases the lesion was complicated with cardiac disease. Opie[2] reported 39 cases of zonal necrosis, central in 12 of them, in 500 autopsies. In 6 of these 12 the central capillary vessels were markedly dilated, and in 8 the heart and blood vessels presented lesions. Previously the main emphasis had been placed on exogenous hepatotoxic substances of bacterial or chemical origin, whereas more recently endogenous factors, such as hyperthyroidism[3] and especially passive congestion, have been accused. In human autopsy material it is difficult to exclude the effect of a terminal infection or of

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1. (*a*) Mallory, F. B.: J. M. Research **6**:264, 1901; (*b*) **24**:455, 1911. (*c*) Lambert, R. A., and Allison, B. R.: Bull. Johns Hopkins Hosp. **27**:350, 1916. (*d*) Oertel, H.: Arch Int. Med. **6**:294, 1910.

2. Opie, E. L.: J. M. Res. **12**:147, 1904.

3. McIver, M. A.: Surgery **12**:654, 1942.

toxic substances. In animal experiments [4] central necrosis without inflammatory reaction has been produced by congestion without infections or toxins. The claim was originally made [5] that morphologic differences exist between simple chronic congestion with atrophy of the liver cells and central necrosis; the latter, if occurring in cases of heart failure, was considered due to complicating hepatotoxic factors. However, in more recent years centrolobular atrophy has been considered the result of chronic passive congestion of gradual onset and true necrosis the result of abrupt or severe protracted heart failure in the absence of other complicating factors.[6] Himsworth [7] in a recent intriguing treatise emphasized the circulatory or vascular factor in the pathogenesis of all types of hepatic necrosis. According to him, both the massive and the zonal form are caused by swelling of the epithelial liver cells. The former is due to complete arrest of the circulation; the latter, to impairment of the circulation in the central portion of the lobule. Both can be produced by the same agent and vary only in the extent of the lesion. In his opinion, toxic substances produce damage of liver cells by an interference with the intralobular circulation similar to that produced directly by heart failure.

## MATERIAL AND METHOD

In approximately 2,000 autopsies 100 instances of central necrobiosis, necrosis, atrophy or disappearance of liver cells were noted. Those with fibrotic or cirrhotic changes were excluded, as were instances in which further analysis revealed primary hepatic or biliary tract diseases as the cause of death. The latter restriction was chosen to equalize as much as possible the degree of hepatic involvement. The histologic description was made in all cases without knowledge of the remainder of the autopsy results or clinical manifestations. After the description was completed, the cases were divided into five groups on the basis of available clinical records correlated with the gross anatomic findings: 1. Twenty cases in which heart failure was not a factor. In this group another factor, chemical or bacterial, was obviously responsible for the damage of the liver. To simplify description, these factors will be referred to as "toxic" in lieu of a better term. 2. Seven cases in which the primary cause of death was extracardiac but in which heart failure was a terminal event. Cases in which passive congestion was an anatomic but not a clinical finding were placed in this group. 3. Twenty-six cases in which heart failure in addition to other diseases was important as a cause of death. 4. Thirty cases in which heart failure was the primary cause of death

4. (*a*) Bolton, C. J.: J. Path. & Bact. **19**:258, 1914. (*b*) Zimmerman, H. M., and Hillsman, J. A.: Arch. Path. **9**:1154, 1930. (*c*) Simonds, J. P., and Callaway, J. W.: Am. J. Path. **7**:578, 1931.

5. Frothingham, C. J.: Arch. Int. Med. **5**:1, 1910. Mallory.[1b]

6. Boland, E. W., and Willius, F. A.: Arch. Int. Med. **62**:723, 1938. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1942. Lambert and Allison.[1c]

7. Himsworth, H. P.: The Liver and its Diseases, Cambridge, Mass., Harvard University Press, 1947.

but in which terminal findings appeared which may have had a toxic effect on the liver, e. g., hypostatic bronchopneumonia. 5. Seventeen cases in which heart failure alone was responsible for death. The differences in the gross and the microscopic appearance of the liver between the first and the last group were analyzed and an attempt was made to extract characteristics for determining whether the disappearance of the central liver cells was the result of a hepatotoxic influence or of passive congestion. These criteria were then applied to the intermediate groups of cases. Hematoxylin-eosin sections of material fixed for the most part in Carnoy's solution were studied, often supplemented with sections prepared with Mallory's aniline blue connective tissue stain.

## RESULTS

*Group Without Evidence of Heart Failure.*—In this group the following conditions caused death: carcinoma, 4 cases; peritonitis, 3 cases; bronchopneumonia, 3 cases; acute gastrointestinal disease, 3 cases; miliary tuberculosis, 2 cases; pulmonary tuberculosis, 1 case; tuberculosis meningitis, 1 case; postoperative atelectasis, 1 case; uremia, 1 case, and subarachnoid hemorrhage, 1 case. Grossly, the liver was larger than usual. The edges were round, and the lobular markings were rather distinct, owing to a darker color of the central portion of the lobule. On close inspection this zone revealed an irregular outline. Bridges connecting the darker zones were seldom seen. Histologically (fig. 1 *A*), the structure of the liver cell cords in the central zone was missing. The liver cells were either absent or isolated and rounded. Their cytoplasm revealed irregular clumps of coagulated protein and fat droplets. The structural details of the cells were still apparent, even in cells without nuclear staining. Large fragments of liver cells were also found. Remnants and fragments were surrounded by a varying number of exudative cells, some of them mononuclear and phagocytic, others polymorphonuclear in nature. The perisinusoidal spaces were usually wide and filled with albuminoid debris (fig. 1 *B*). The sinusoids themselves varied in width and often contained fibrinous thrombi. The Kupffer cells were phagocytic. The central and sublobular veins were narrow and appeared thick-walled. The relation between width of lumen and wall was best appreciated where capillaries or small venules pierced through the wall of the larger vein. The intramural portion was narrow, giving the impression of being compressed by contraction of the wall of the larger vessel (fig. 1 *C*). The portion of the smaller vessel which immediately preceded the point at which the vessel entered the wall of the larger vein was usually much wider than the intramural portion. The inner outline of the larger vein was often irregular. The border between the necrotic zone, which did not exceed one third of the lobule, and the preserved parenchyma was usually not sharp, and the cells of the central portion of the intact part on many occasions revealed fatty changes and were surrounded by edema fluid. Focal necroses were occasionally found.

*Group in Which Fatal Heart Failure Occurred Without Complicating Toxic Factors.*—The liver was not always grossly enlarged, and its free edge was not regularly blunted. The lobular markings were distinct but varied throughout the liver. In many areas the central depressed zones of the lobules were connected with each other by definite bridges, leading to reversal of the lobular pattern. This produced light central zones, indicating intact periportal parenchyma and depressed peripheral zones, the result of communicating central portions of the lobules. Histologically, the liver cell cords in the central zone were either missing or distorted and narrowed. The cytoplasm of these compressed portions appeared denser and strongly basophilic. Their nuclei were usually rich in chromatin and well preserved (fig. 2 *A*). Cell fragments or remnants were completely absent. The sinusoids

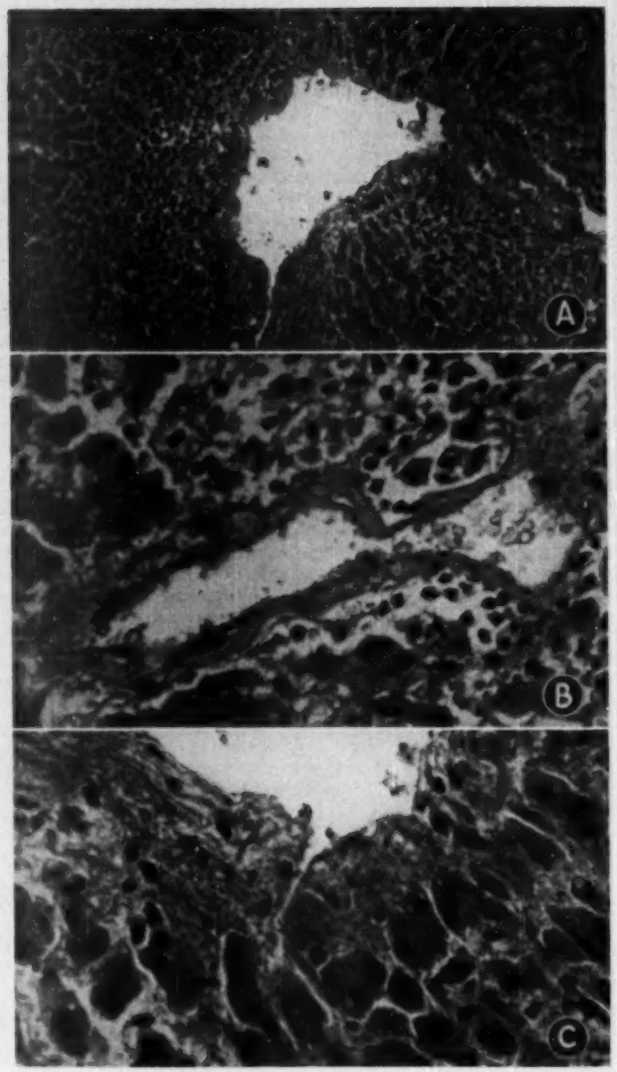


Fig. 1.—Central necrosis in the group of cases in which there was no evidence of heart failure. *A*, low power view revealing anuclear cell fragments and exudative cells surrounding a sublobular vein. A piercing vein is seen entering the lower portion of the larger vein (× 175). *B*, anuclear cell fragments are grouped around a central vein. Polymorphonuclear and other exudative cells have accumulated in the necrotic area (× 710). *C*, narrow piercing vessel which appears compressed by the intramural portion of the larger vessel. The structure of the surrounding liver cell cords is disturbed. Anuclear cell fragments are noted (× 710).

were slightly to markedly dilated and engorged with red cells. Fibrinous thrombi were often found in the sinusoids but only rarely in the wide perisinusoidal spaces. Exudative cells were rare. The central veins appeared wide, their inner lining straight. The intramural portions of the smaller vessels piercing through the

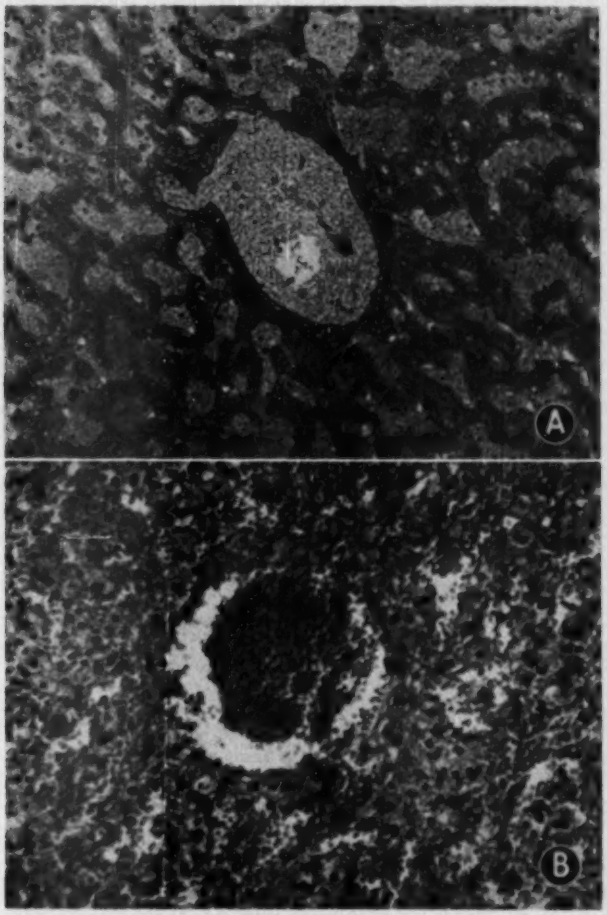


Fig. 2.—Central necrosis in the group of cases in which fatal heart failure occurred without complicating toxic factors. *A*, dilatation of sinusoids and atrophy of liver cells. The central vein is dilated, and the piercing vessels are wide open (× 175). *B*, central disappearance and atrophy of liver cells. Exudative cells are absent, and open piercing veins enter upper and lower right portions of the central vein (× 360).

central vein did not appear compressed and were equal in width to the preceding portions of the small vessels (fig. 2 *B*). The borderline between the necrotic area and the intact zone was sharp, and the adjacent cells were free of degenerative changes. The sinusoids in the intact area were not necessarily dilated. Focal necroses were rarely found.

*Correlation of Histologic Phenomena in the Remaining Three Groups.*—In the remaining three groups the histologic picture revealed a combination of the manifestations noted in the two previous groups (table 1). Of the five histologic characteristics which were more prominent in cases with a predominance of "toxic" manifestations, namely, small central veins, narrow piercing veins, liver cell fragments, exudative cells and definite dissociation of liver cell cords, the first three presented the most striking group differences, while the relative incidence of the last two was somewhat less impressive. Disappearance of cells and dilatation of sinusoids were more characteristic of the group with predominantly congestive manifestations. The following characteristics did not vary significantly in the groups: irregular staining of nucleus and cytoplasm, fibrinous thrombi, Kupffer cell mobilization, connective tissue collapse, edema, exudative cells in the portal triads, bile duct proliferation, hemosiderin and lipofuscin deposition. Focal necroses were not prominent in any group but were relatively more frequent in cases with mainly "toxic" manifestations. Fatty changes were found in both groups, but since they are influenced by a great variety of factors, such as state of nutrition and intestinal absorption, they were deliberately omitted. The frequency of each of the significant histologic characteristics varied in each of the clinical–gross anatomic groups. The highest numerical incidence of the five characteristics listed in this paragraph as more prominent in the "toxic" cases is found in the "toxic" group and the lowest in the congestive group, the other groups revealing a gradual transition (table 2).

TABLE 1.—*Percentage Incidence of Various Histologic Changes in the Different Groups Established by Correlation of Clinical and Gross Anatomic Findings*

| Histologic Change | Percentage of Cases in Which Given Change Was Present | | | | |
|---|---|---|---|---|---|
| | Pure "Toxic" Group | Predominantly "Toxic" Group | Mixed Group | Predominantly Congestive Group | Pure Congestive Group |
| Narrowed piercing veins | 60 | 100 | 69 | 29 | 0 |
| Small central veins | 65 | 71 | 38 | 3 | 0 |
| Abundant liver cell fragments and remnants | 85 | 57 | 54 | 7 | 0 |
| Presence of exudative cells | 65 | 86 | 73 | 20 | 24 |
| Definite dissociation of liver cells | 80 | 71 | 65 | 37 | 37 |
| Marked disappearance of liver cells | 15 | 29 | 38 | 23 | 47 |
| Dilatation of sinusoids | 50 | 29 | 69 | 90 | 100 |
| Total number of cases in each group | 20 | 7 | 26 | 30 | 17 |

*Significance of Individual Hepatotoxic Etiologic Factors.*—The hepatotoxic etiologic factors were evaluated in cases in which only one such factor was elicited (table 3). Any one of those factors was associated in about half of the cases with at least three of the five histologic phenomena previously found characteristic for the "toxic" cases. The highest number of these phenomena

was found in the presence of acute diseases of the gastrointestinal tract, which included suppurative peritonitis, acute pancreatitis and acute gastroenteritis. The lowest number was found in the presence of emboli or infarcts.

*Relation to Jaundice.*—Jaundice was present in 13 cases of central necrosis. However, no evidence could be found that it was correlated with any of the so-called "toxic" changes.

TABLE 2.—*Numerical Incidence of the Five Different Histologic Changes* Which Are Characteristic of "Toxic" Causation Occurring in Individual Cases of the Different Groups Established by Correlation of Clinical and Gross Anatomic Findings*

| Number of Histologic Changes | Number of Cases in Which Given Number of Changes Were Present | | | | |
|---|---|---|---|---|---|
| | Pure "Toxic" Group | Predominantly "Toxic" Group | Mixed Group | Predominantly Congestive Group | Pure Congestive Group |
| 0 | 0 | 0 | 0 | 12 | 7 |
| 1 | 0 | 0 | 5 | 12 | 9 |
| 2 | 4 | 1 | 3 | 3 | 1 |
| 3 | 5 | 2 | 9 | 3 | 0 |
| 4 | 7 | 1 | 6 | 0 | 0 |
| 5 | 4 | 3 | 3 | 0 | 0 |
| Total number of cases in each group | 20 | 7 | 26 | 30 | 17 |

* These are narrow piercing veins, small central veins, liver cell fragments, exudate cells and dissociation of liver cell cords.

TABLE 3.—*Hepatotoxic Etiologic Factors and Their Incidence and Significance, The Latter Being Judged from the Incidence of the Morphologic Changes* Pointing to a "Toxic" Causation*

| Hepatotoxic Etiologic Factors | Number of Cases | Number of Cases Without Other Hepatotoxic Factors | Number of Cases of Previous Column with 3 or More "Toxic" Histologic Changes |
|---|---|---|---|
| Acute gastrointestinal disease | 10 | 6 | 4 |
| Miscellaneous | 11 | 6 | 5 |
| Bronchopneumonia | 27 | 9 | 5 |
| Uremia | 18 | 12 | 7 |
| Infections (including tuberculosis) | 17 | 13 | 7 |
| Emboli or infarcts | 21 | 11 | 5 |

* These are narrow piercing veins, small central veins, liver cell fragments, exudative cells and dissociation of liver cell cords.

## COMMENT

As a result of correlating the histologic changes in the two selected "pure" groups of cases, those in which congestive heart failure was the cause of death, and those in which hepatotoxic factors were present without heart failure, two different histologic entities can be recognized. The characteristic findings occurred in the transitional groups in corresponding incidence. In the first group, usually associated with heart

failure, were the following characteristic findings: (1) atrophy of surviving liver cells, (2) marked dilatation of sinusoids, (3) wide central veins, (4) wide or normally open small veins piercing through the wall of the central vein and (5) disappearance of liver cells without visible cell fragments. In the second group, most often associated with exposure to substances injurious to the liver (called "toxic"), the characteristic findings were: (1) anuclear cell fragments and remnants, (2) exudative cells encircling the fragments, (3) despite occasionally wide sinusoids, narrow central veins revealing contraction of the small vessels piercing the central vein. Similar but more impressive changes have been observed in fatal toxic hepatitis, including cases due to drug poisons.[8]

The atrophy of the liver cells which occurs in the centers of the lobules in heart failure can be explained partially by hydrodynamic pressure and partially by nutritional deficiency due to impaired blood flow. It is not necessarily associated with impaired function of the cell, since basophilia of the cytoplasm of the liver cell (an indication of its ribonucleic acid content and therefore of cell vitality) is not decreased in these cases, but increased, apparently due to condensation.[9] The atrophic cells seem to disappear without any remnants.

In contrast, the large remnants or fragments of cells seen in the "toxic" form may reveal clumps of coagulated protein with increased eosinophilia due to loss of ribonucleic acid. The deterioration of the hepatic parenchyma may attract exudative cells, chiefly segmented leukocytes. Apparently these fragments are more slowly removed than are the necrotic cells in the heart failure cases, or they may have been formed shortly before death. That fragments exist in the course of congestive heart failure obviously cannot be excluded, but because of the more chronic character of the process, they may be less common histologically.

It is not easy to prove the contraction of the tributaries of the hepatic vein in the "toxic" cases since the width of the tributary depends on its distance from the main stem of the hepatic vein. One might better rely on the relation between lumen and wall, but even that criterion is not completely reliable inasmuch as the wall may be widened by fibrosis or edema. The relation of the veins running through the wall of the hepatic vein tributary was the most reliable criterion. If these piercing branches were narrowed in passing through the wall of the larger vessel and particularly if they were dilated before they entered into the larger vessel, it appeared justified to assume that there had been contraction of the larger vessel. The existence of a sphincter mechanism of the hepatic

8. Popper, H., and Franklin, M.: Arch. Path. **46**:338, 1949.

9. Szanto, P. B., and Popper, H., to be published.

veins has been disputed in the literature.[10] However, its presence seems to be established in human and especially animal livers.[11] The contracted central veins and narrow piercing veins characteristic of the "toxic" type of central necrosis impair the intralobular blood flow. This may be a contributing factor in the central necrosis and may be the cause of the fibrin thrombi so commonly found in this condition.

Most of the hepatotoxic factors encountered in this study have already been listed by Mallory. To these are to be added uremia and infarcts. In cases in which pulmonary infarcts are present, infection,[12] toxic substances liberated from the infarct [13] and anoxemia [14] have been assumed and are probably more responsible for the jaundice occasionally seen in this condition than are blood breakdown products.[15]

Central necrosis may be produced by congestive failure of the circulatory system as well as by exogenous or endogenous injurious agents. However, in contrast to the opinion of Himsworth,[7] it appears that the histologic characteristics of the "congestive" and "toxic" groups differ sufficiently to be of diagnostic aid in the interpretation of the disease process. The central localization of the necrosis is obviously due to disturbance of the circulation in the center of the lobule, resulting in decreased oxygen tension and impaired neutralization of poisons. The fibrinous thrombi in both "toxic" and "congested" cases are morphologic evidence for stasis. In passive congestion this central stasis is caused by impaired blood return to the heart [16]; in the "toxic" cases, by contraction of the smaller hepatic vein branches and probably also by swelling of the hepatic cells.[7] This localizing factor is enhanced in the "toxic" cases by the effect of the injurious substance itself, while in the "congestive" cases the greatly increased venous pressure plays a part. The effect of the latter is probably not as great in chronic as in acute congestion.[17] A degree of anoxia which ordinarily produces only minor

10. (*a*) Arey, L. B., and Simonds, J. P.: Anat. Rec. **18**:219, 1920. (*b*) Bauer, W.; Dale, H. H.; Poulson, L. T., and Richards, D. W.: J. Physiol. **74**:343, 1932. (*c*) Popper, H.: Klin. Wchnschr. **10**:2129, 1931. (*b*) Arey, L. B.: Anat. Rec. **81**:21, 1941. (*e*) Wakim, K. G., and Mann, F. C.: Ibid. **82**:233, 1942. (*f*) Knisely, M. H.: Proc. Inst. Med. Chicago **16**:286, 1947.

11. Deysach, L. J.: Am. J. Physiol. **132**:713, 1941. Snyder, C. D.: Rev. Gastroenterol. **9**:230, 1942. Bauer and others.[10b]

12. Kugel, M. A., and Lichtman, S. S.: Arch Int. Med. **52**:16, 1933.

13. Popper, H.: Virchows Arch. f. path. Anat. **298**:574, 1937.

14. Rich, A. R., and Resnik, W. H.: Bull. Johns Hopkins Hosp. **38**:75, 1926.

15. Resnik, W. H., and Keifer, C. S.: J. Clin. Investigation **2**:389, 1926. Rich and Resnik.[14]

16. Young, L. E.: New England J. Med. **237**:225, 1947. Costero, J.: Am. Heart J. **33**:701, 1947.

17. Lambert and Allison.[1c] Bolton.[4a] Zimmerman and Hillsman.[4b]

changes causes central degeneration similar to the "toxic" alterations in this series in hyperthyroidism in animals.[18]

The lack of correlation of clinical and functional manifestations, including jaundice, with the extent of hepatic necrosis has previously been stressed.[19] In comparing biopsy specimens of liver with autopsy material obtained shortly after the biopsy, it has been found that central necrosis may be an agonal lesion.[20]

Knowledge of the significance of the central necrosis is important for the understanding of the morphologic changes of diseases with established hepatic injury. Apparently even in this group, which includes cirrhosis and fatal toxic hepatitis, the localizing effect of circulatory disturbances, as well as that of hepatotoxic substances, is responsible for the central necrosis

SUMMARY

On the basis of clinical and gross anatomic findings, 100 cases in which autopsy revealed central hepatic necrosis (not including primary hepatic disease) were divided into five groups. One group included cases in which death was from heart failure alone, while another included those in which heart failure was not a factor in the fatal outcome but some other factor, toxic or infectious, was the cause of death. The remaining three groups represented transitions between the "pure" groups. Different histologic changes in the liver were found associated with the "pure" clinical groups and were found in corresponding incidence in the transitional groups. The "congestive" cases were characterized by : (1) large central veins, (2) wide or normally open branches piercing through the walls of the larger vessels, (3) marked disappearance and atrophy of liver cells but no fragments or remnants of cells, and (4) usually dilatation of sinusoids. The "toxic" cases were distinguished by (1) anuclear cell fragments, (2) exudative cells encircling the fragments, (3) despite occasionally wide sinusoids, small central veins with (4) narrow piercing branches, and (5) dissociation of liver cell cords. Intralobular circulatory disturbances were considered important in the localization of the necrosis in the central portion of the liver lobule in all instances. In the "congestive" cases this disturbance is caused by heart failure, while in the "toxic" cases it is secondary to central vein contraction and probably swelling of the liver cells. Other factors in the production of the necrosis were increased venous pressure in the "congestive" cases and the injurious substance itself in other instances. The hepatotoxic factors most commonly found were uremia, pulmonary or myocardial infarcts, acute gastrointestinal disease, bronchopneumonia and other infections.

18. McIver, M. A., and Winter, E. A.: Arch. Surg. **46**:171, 1943.
19. Lambert and Allison.[16] Bolton.[48] Kugel and Lichtman.[13]
20. Popper, H.: Arch. Path. **46**:1, 1948.

# GLOMERULONEPHROSIS

## A Morphologic Manifestation of Renal Cortical Ischemia in Toxic Oliguria and Lower Nephron Nephrosis

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THE MINIMAL morphologic changes in the renal tubular epithelium in cases of so-called lower nephron nephrosis have not been considered to be sufficient to explain the oliguria or anuria accompanying this syndrome. Bell [1] has emphasized the concept of glomerulonephrosis, a term which had been introduced by Fahr [2] as descriptive of the glomerular change in cases of eclampsia. I have found similar glomerular changes in many cases of lower nephron nephrosis and have verified their occurrence in 10 of 11 cases of eclampsia. It appeared to be essential to the explanation of oliguria and anuria in cases of lower nephron nephrosis that a glomerular lesion be demonstrated, since tubular change alone in the presence of normal renal blood flow and glomerular filtration rate would be associated with polyuria rather than with a reduction of urinary output.

### LITERATURE

Trueta [3] has presented the physiologic evidence for the concept of an ischemic glomerulus in toxic oliguria and anuria, and Bell [1] has emphasized the morphologic changes in the glomerular capillary tufts in cases of eclampsia, as described by Leusden,[4] Löhlein [5] and Fahr.[2] Lauson, Bradley and Cournand [6] utilized clearance methods to confirm the hypothesis that urinary oliguria or anuria was attributable to shock with decreased circulation through the kidney and, specifically, a decrease in glomerular filtration pressure, which was greater than the reduction of arterial pressure would explain.

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From the Department of Pathology, University of Michigan.
Presented at the Forty-Sixth Annual Meeting of the American Association of Pathologists and Bacteriologists, Boston, April 15, 1949.

1. Bell, E. T.: Renal Diseases, ed. 5, Philadelphia, Lea & Febiger, 1946.
2. Fahr, T.: Zentralbl. f. Gynäk. **44**:991, 1920; **52**:474, 1928.
3. Trueta, J.: Studies of the Renal Circulation, Springfield, Ill., Charles C Thomas, Publisher, 1947.
4. Leusden, P.: Virchows Arch. f. path. Anat. **142**:1, 1895.
5. Löhlein, M.: Deutsche med. Wchnschr. **44**:1187, 1918.
6. Lauson, H. D.; Bradley, S. E., and Cournand, A.: J. Clin. Investigation **23**:381, 1944.

In his earlier work Goormaghtigh [7] did not report a glomerular lesion of the type stressed by Bell,[1] but in a later report he stated that in cases of fatal crush syndrome or traumatic anuria the glomerular changes were identical with those seen in cases of eclampsia, anuria and fulminating glomerulonephritis. However, he did not illustrate or elaborate on these glomerular changes. Kaufmann [8] and Oberling [9] were impressed by the juxtaglomerular apparatus, but they did not report glomerular changes.

Thompson, Frazier and Ravdin [10] recognized glomerular changes associated with obstructive jaundice but interpreted them as evidences of nephrosclerosis. Lieber and Stewart [11] did not describe glomerular changes in cases of hepatitis but, like Lucké [12] and Lucké and Mallory,[13] stated that cholemic nephrosis was not associated with uremia or other evidence of serious renal damage. Elsom [14] reported nephrosis but did not note glomerular changes in cases of obstructive jaundice and found that the evidences of renal injury disappeared as the jaundice subsided. Ayer,[15] however, reported renal lesions, comparable to those seen in transfusion reactions and in the hepatorenal syndrome, in cases in which cholemic nephrosis was associated with congenital biliary atresia and resultant biliary cirrhosis in infants and children.

Glomerular lesions were not described by Kimmelstiel [16] in 6 cases of acute hematogenous interstitial nephritis following transfusions of incompatible blood. He attributed the eosinophilia to a hyperergic phenomenon resulting from foreign protein or protein-split products. Likewise, Bell and Knutson [17] did not refer to glomerular changes in 84 cases of terminal azotemia; nor did Snell and Butt,[18] Helwig and Orr,[19] Schutz, Helwig and Kuhn,[20] Boyce and McFetridge [21] and Heyd [22] in their discussions of the hepatorenal syndrome. Bywaters and Beall,[23]

7. Goormaghtigh, N.: Am. J. Path. **16**:409, 1940; **23**:513, 1947.
8. Kaufmann, W.: Am. J. Path. **18**:783, 1942.
9. Oberling, C.: Am. J. Path. **20**:155, 1944.
10. Thompson, L. L., Jr.; Frazier, W. D., and Ravdin, I. S.: Am. J. M. Sc. **199**:305, 1940.
11. Lieber, M. M., and Stewart, H. L.: Arch. Path. **19**:636, 1935.
12. Lucké, B.: (*a*) Am. J. Path. **20**:471, 1944; (*b*) Mil. Surgeon **99**:371, 1946.
13. Lucké, B., and Mallory, T. B.: Am. J. Path. **22**:867, 1946.
14. Elsom, K. A.: Arch. Int. Med. **60**:1028, 1937.
15. Ayer, D.: Arch. Path. **30**:26, 1940.
16. Kimmelstiel, P.: Am. J. Path. **14**:737, 1938.
17. Bell, E. T., and Knutson, R. C.: J. A. M. A. **134**:441, 1947.
18. Snell, A. M., and Butt, H. R.: Tr. A. Am. Physicians **56**:321, 1941
19. Helwig, F. C., and Orr, T. G.: Arch. Surg. **24**:136, 1932.
20. Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: J. A. M. A. **99**:633, 1932.
21. Boyce, F. F., and McFetridge, E. M.: Arch. Surg. **31**:105, 1935.
22. Heyd, C. G.: Ann. Surg. **79**:55, 1924.
23. Bywaters, E. G. L., and Beall, D.: Brit. M. J. **1**:427, 1941.

Bywaters and Dible,[24] Mallory [25] and Coller, Campbell and Iob [26] stressed the tubular lesions in traumatic anuria but did not mention glomerular changes. Darmady [27] listed many pathologic states that might result in "traumatic anuria," and many of our cases could be included in this grouping.

TABLE 1.—*Clinical and Gross Necropsy Data for the Cases Selected for the Study Group*

| Patient | Age | Sex | Main Diagnoses and Notes on Treatment | Blood Nonprotein Nitrogen, Mg. per 100 Cc. | Interval Between Death and Autopsy, Hr. | Ascites | Jaundice | Weight of Kidneys, Gm. | Weight of Heart, Gm. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | M | Syphilis; arsenical therapy; atrophy of liver | 0 | 1 | + | + | 160-L 160-R | 310 |
| 2 | 49 | F | Biliary cirrhosis; choledocholithiasis | 45 | 1 | + | + | 165-L 160-R | 215 |
| 3 | 50 | F | Atrophic cirrhosis | 0 | 4 | + | + | 140-L 150-R | 250 |
| 4 | 55 | M | Carcinoma of stomach; protein hydrolysate ("amigen") | 85 | 6 | 0 | 0 | 230-L 220-R | 340 |
| 5 | 43 | M | Myeloid leukemia; urethane therapy | 0 | 4 | 0 | 0 | 220-L 225-R | 430 |
| 6 | 65 | M | Myeloid leukemia; urethane therapy | 205 | 7 | 0 | 0 | 270-L 490-R | 370 |
| 7 | 70 | F | Biliary cirrhosis; choledocholithiasis | 0 | 1 | + | + | 145-L 155-R | 280 |
| 8 | 63 | F | Carcinoma of stomach; metastasis to liver; transfusion reaction | 160 | 4 | + | + | 210-L 200-R | 340 |
| 9 | 36 | M | Ruptured cerebral arterial aneurysm | 0 | 2 | 0 | 0 | 200-L 160-R | 220 |
| 10 | 45 | F | Acute peritonitis; ileostomy | 0 | 1 | Acute peritonitis | 0 | 140-L 150-R | 300 |
| 11 | 59 | F | Homologous serum hepatitis | 73 | 7 | 0 | + | 200-L 190-R | 320 |
| 12 | 32 | F | Abortion; acute hepatitis | 41 | 13 | 0 | + | 340-L 340-R | 260 |
| 13 | 21 | M | Hodgkin's disease; nitrogen mustard therapy | 0 | 7 | + | + | 220-L 190-R | 230 |
| 14 | 62 | F | Carcinoma of endometrium | 0 | 18 | 0 | 0 | 220-L 190-R | 280 |
| 15 | 48 | M | Fractured skull; sulfonamide hypersensitivity | 205 | 3 | 0 | 0 | 200-L 210-R | 280 |
| 16 | 58 | M | Carcinoma of bladder | 42 | 9 | 0 | 0 | 120-L 100-R | 350 |
| 17 | 71 | F | Carcinoma of rectum; sulfonamide hypersensitivity | 158 | 2 | + | + | 58-L 120-R | 200 |
| 18 | 41 | M | Automobile accident; crush syndrome | 205 | 2 | 0 | + | 225-L 230-R | 290 |
| 19 | 43 | M | Hodgkin's disease | 130 | 6 | + | + | 280-L 300-R | 340 |
| 20 | 47 | M | Gastric ulcer; acute peritonitis | 168 | 4 | Peritonitis | 0 | 165-L 150-R | 220 |

24. Bywaters, E. G. L., and Dible, J. H.: J. Path. & Bact. **54**:111, 1942.
25. Mallory, T. B.: Am. J. Clin. Path. **17**:427, 1947.
26. Coller, F. A.; Campbell, K. N., and Iob, V.: Ann. Surg. **128**:379, 1948.
27. Darmady, E. M.: J. Bone & Joint Surg. **30-B**:309, 1948.

Some of the toxic changes associated with the administration of amino acids have been noted by Hopps and Campbell [28] and by Curreri, Hibma and Cohen,[29] but glomerular lesions were not described.

## MATERIAL

For this report, a detailed histologic study was made of the kidneys of 20 specially selected patients from the University Hospital (table 1). This group did not include the patients with eclampsia to whom reference has been made. Both clinical and necropsy records were reviewed in an effort to exclude all who might have had primary or secondary renal disease from causes other than those which are considered provocative of the lower nephron syndrome. In an attempt to

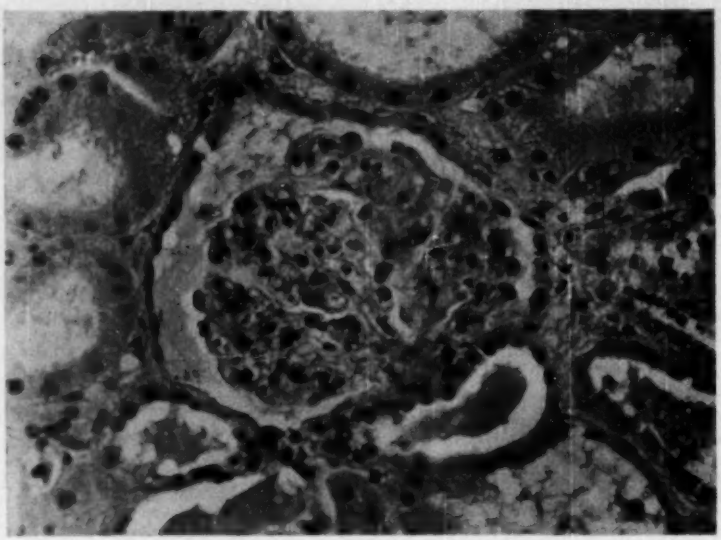

Fig. 1 (case 4).—Glomerular ischemia with thickening of capillary walls, protein precipitate, and casts in Bowman's capsular spaces and tubules in a patient with carcinoma of the stomach and metastases in the liver. Protein hydrolysate (amigen®) had been administered, 1 liter per day, for seven days before death.

eliminate renal changes associated with cardiovascular hypertension, patients were omitted in whom the heart weighed more than 420 Gm. if that of a male and 350 Gm. if that of a female. Eighty additional patients who showed glomerulonephrosis were eliminated from the study because of other complicating diseases.

Two thirds of the patients admitted to the study group were those in whom an advanced lesion was present, comparable to grade 3 of Bell's [1] study. The main clinical diagnoses for the accepted patients, confirmed at necropsy, were biliary

28. Hopps, H. C., and Campbell, J. A.: J. Lab. & Clin. Med. **28**:1203, 1943.
29. Curreri, A. R.; Hibma, O. V., and Cohen, P. P.: J. A. M. A. **128**:732, 1945.

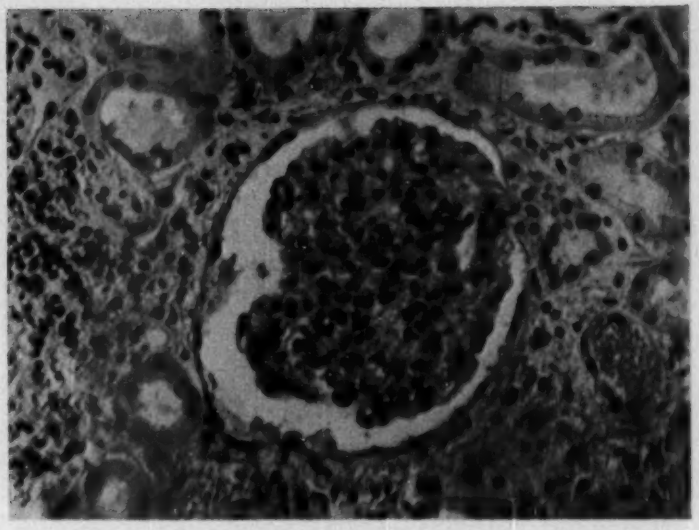

Fig. 2 (case 18).—Ischemic glomerulus with thickened capillary walls in a patient with the crush syndrome resulting from an automobile accident.

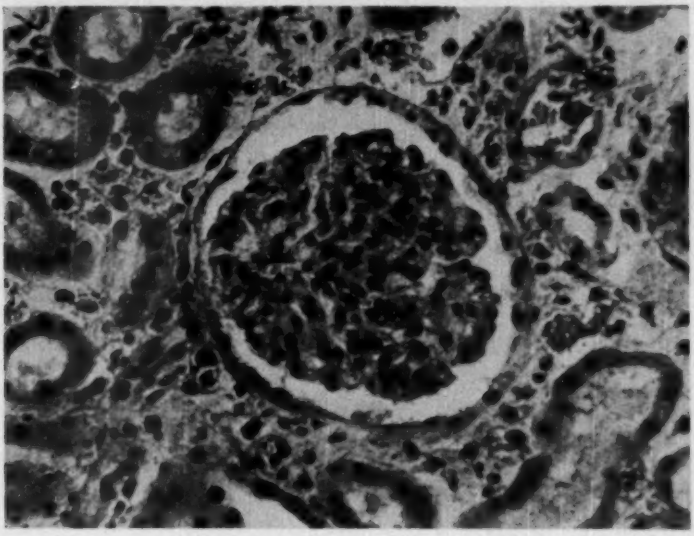

Fig. 3 (case 16).—Glomerular ischemia with thickening of capillary walls and slight hypertrophy of the epithelium of Bowman's capsule in a patient with carcinoma of the bladder and sulfonamide hypersensitivity.

cirrhosis, sulfonamide hypersensitivity, acute peritonitis, myeloid leukemia, lymphoblastoma of Hodgkin's disease type, arsenical acute yellow atrophy of the liver, atrophic cirrhosis, shock associated with ruptured congenital aneurysm of the cerebral artery, homologous serum hepatitis, transfusion reaction, acute hepatitis associated with septic abortion, crush syndrome, carcinoma of the bladder, carcinoma of the endometrium and amigen therapy. The first five diagnoses were made in 2 cases each.

The average age of the 20 patients at the time of death was 49 years, the oldest being 71 and the youngest 22 years of age. Infants and children had been eliminated to facilitate the evaluation of the weights of organs. Eleven of the patients were men.

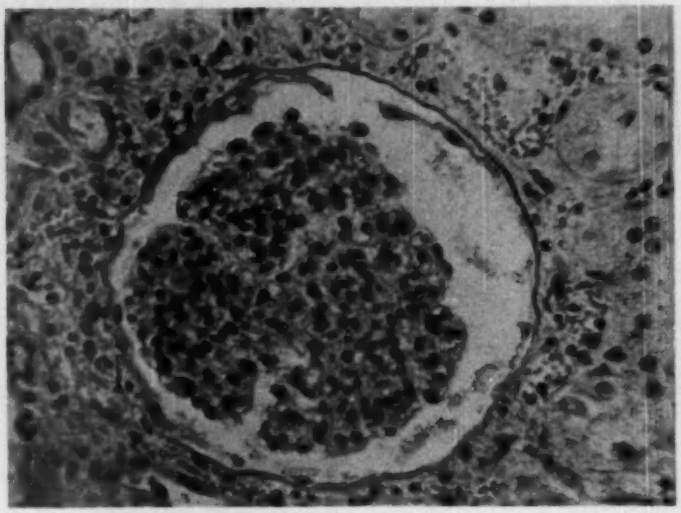

Fig. 4 (case 12).—Glomerular ischemia and thickening of capillary walls in a patient who had undergone abortion and acute hepatitis.

Necropsy was performed within four hours after death in most instances, although more than six hours had elapsed in 4 cases. If these 4 cases had been eliminated, the average time which had elapsed between death and necropsy would have been three hours.

Ascites was present in 3 men and 5 women; jaundice was found in 4 men and 7 women. The blood nonprotein nitrogen was significantly increased in 9 of the 12 cases in which it had been determined. The range varied from 41 to 385 mg. per hundred cubic centimeters; the average level for the 9 cases was 195 mg. per hundred cubic centimeters.

The average weight of the left kidney was 195 Gm., and that of the right kidney 203 Gm. The material was too limited for statistical evaluation, but 1

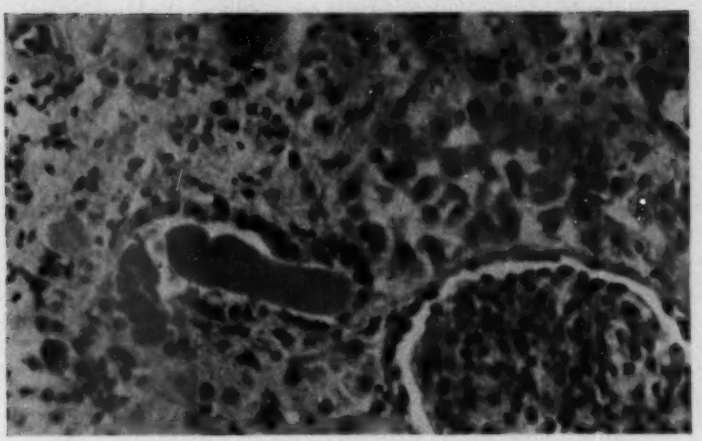

Fig. 5 (case 18).—Tubules with protein casts. Ischemic glomerulus with thickened capillary walls.

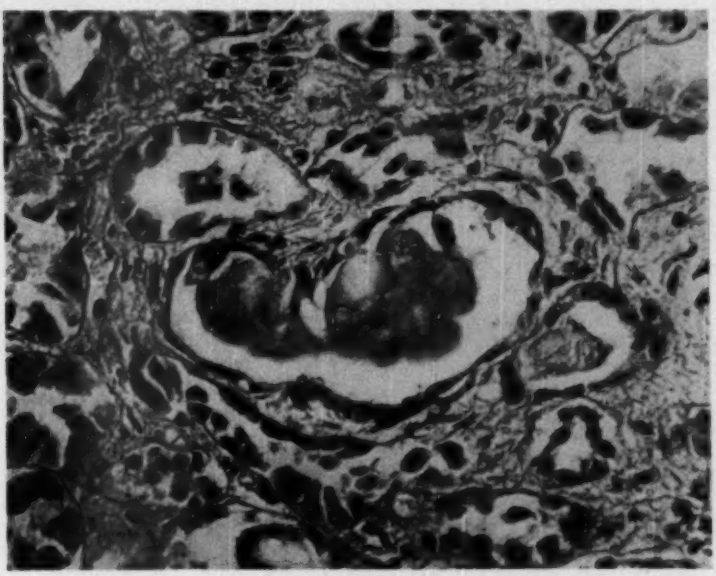

Fig. 6 (case 4).—Protein cast in distal convoluted tubule.

case of neoplastic disease was responsible for the obvious discrepancy between the weights of the left and right kidneys. The average weight of the heart was 286 Gm. for women and 315 Gm. for men.

### HISTOPATHOLOGIC CHANGES (TABLE 2)

*Glomeruli.*—The glomeruli (figs. 1 to 5), as indicated by Löhlein [5] and confirmed by other authors cited in the foregoing pages, showed thickening of the walls of the capillaries, decreased blood content, at times swelling of the glomerular epithelium (not conspicuous in most of the material) and slightly increased numbers of intracapillary cells. This last finding was not a striking feature in association with either hypertrophic or atrophic glomeruli, and, as indicated by Bell,[1] decreased glomerular endothelial cellularity and relative ischemia were the rule.

TABLE 2.—*Microscopic Changes in the Glomeruli*

| Case | Ischemia of Capillaries* | Hypertrophy | Atrophy | Epithelial Proliferation* | Protein in Capsular Space* |
|---|---|---|---|---|---|
| 1 | 4 | 0 | 0 | 0 | 0 |
| 2 | 4 | 0 | 0 | 0 | 0 |
| 3 | 4 | 0 | 0 | 0 | 1 |
| 4 | 4 | 0 | 0 | 0 | 0 |
| 5 | 4 | 0 | + | 1 | 0 |
| 6 | 4 | + | 0 | 0 | 0 |
| 7 | 3-4 | 0 | + | 0 | 0 |
| 8 | 3-4 | + | 0 | 1 | 0 |
| 9 | 3-4 | 0 | 0 | 0 | 0 |
| 10 | 4 | 0 | + | 0 | 0 |
| 11 | 4 | + | 0 | 0 | 0 |
| 12 | 4 | + | 0 | 0 | 0 |
| 13 | 3-4 | 0 | 0 | 0 | 0 |
| 14 | 4 | + | 0 | 0 | 4 |
| 15 | 3 | 0 | 0 | 0 | 0 |
| 16 | 3 | 0 | 0 | 0 | 0 |
| 17 | 3 | 0 | 0 | 0 | 1 |
| 18 | 4 | 0 | 0 | 1 | 1 |
| 19 | 4 | + | 0 | 0 | 0 |
| 20 | 3 | + | 0 | 0 | 0 |

* These attributes have been graded quantitatively on a scale of 0 to 4.

The degree of ischemia of the glomerular capillaries and the extent of the associated thickening of their walls suggested grading of the severity of such changes from 1 to 4, in a manner somewhat comparable to the classification of Bell,[1] who utilized grades 1 to 3. In 12 of the 20 cases the changes were graded as 4, or the most severe degree of change, and in 8 cases they were graded 3 or 3 to 4.

With a 10 × wide-angled eyepiece and a 16 mm. objective being used, the occurrence of 5 to 7 glomeruli per low power field near the renal capsular surface was considered to be the norm. In 10 cases the number was normal by this criterion; 7 showed hypertrophy, with a smaller number of larger glomeruli per field, and in 3 the glomeruli were atrophic, with more than 7 glomeruli per low power field.

In none of the cases did the glomeruli show any significant degree of epithelial hyperplasia either of Bowman's capsular lining or of the cells of the external surface of the tufts, although slight proliferation was present in 3 instances.

Gray-blue-staining, somewhat granular, precipitated, protein material was present in the glomerular spaces in 4 cases and in the proximal convoluted tubules in 3. This was interpreted as representing the earliest stage in the formation of the more dense protein casts which will be described as being somewhat characteristic of the well developed case of glomerulonephrosis.

*Tubules.*—In addition to finely granular protein precipitate, three other changes were looked for in the proximal convoluted tubules: cloudy swelling, hydropic change and lipidosis (table 3). In all cases the tubules showed cloudy swelling, which in 2 instances had advanced to simple necrosis. Hydropic change was present in 4 cases and may have represented change in the intracellular protein content, as well as in the fluid content, inasmuch as the cytoplasm was stained more intensely with eosin than it is usually. Lipidosis was present in but 1 instance and then was not a striking feature.

TABLE 3.—*Microscopic Changes in Proximal Convoluted Tubules**

| Case | Protein Casts | Cloudy Swelling | Hydropic Degeneration | Lipidosis | Simple Necrosis |
|---|---|---|---|---|---|
| 1 | 0 | 2 | 0 | 0 | 0 |
| 2 | 0 | 3 | 0 | 0 | 0 |
| 3 | 3 | 4 | 1 | 0 | 0 |
| 4 | 0 | 4 | 0 | 0 | 0 |
| 5 | 0 | 2 | 0 | 2 | 0 |
| 6 | 0 | 2 | 3 | 0 | 2 |
| 7 | 0 | 2 | 0 | 0 | 0 |
| 8 | 0 | 4 | 1 | 0 | 1 |
| 9 | 0 | 4 | 0 | 0 | 0 |
| 10 | 0 | 2 | 0 | 0 | 0 |
| 11 | 0 | 4 | 0 | 0 | 0 |
| 12 | 0 | 4 | 0 | 0 | 0 |
| 13 | 1 | 3 | 0 | 0 | 0 |
| 14 | 4 | 4 | 2 | 0 | 0 |
| 15 | 4 | 4 | 0 | 0 | 0 |
| 16 | 0 | 4 | 0 | 0 | 0 |
| 17 | 0 | 4 | 0 | 0 | 0 |
| 18 | 0 | 2 | 0 | 0 | 0 |
| 19 | 0 | 4 | 0 | 0 | 0 |
| 20 | 2 | 4 | 0 | 0 | 0 |

* All attributes have been graded on a scale of 0 to 4.

The more striking tubular changes (table 4) were present in the distal convoluted tubules, as noted by Lucké [17b] and Mallory [23] in so-called lower nephron nephrosis. Minor degrees of retrogressive changes were present in all cases and were moderately to strikingly advanced in 16 instances. These changes consisted of atrophy, necrosis and regeneration. In 2 cases the regeneration of epithelial cells of the distal convoluted tubules was striking. This was of interest in that Coller, Campbell and Iob [26] have reported recovery in cases of toxic anuria, with regeneration of tubular epithelium and undoubted restoration of glomerular function in seven to fourteen days after injury.

The most constant change in the distal convoluted tubules was the presence of dense gray-blue-stained casts (figs. 1, 5 and 6) which were designated as protein casts in contrast to the hyaline, blood or bile pigment casts which were seen in association with them under special conditions. These casts were abundant in 15 cases of the series, were seen frequently in 4 cases and were absent in 1. Thus

TABLE 4.—*Microscopic Changes in Distal Convoluted Tubules**

| Case | Retrogressive Changes | Lipidosis | Protein Casts | Hyaline Casts | Bile Pigment | Blood Pigment | Sulfonamide Crystals |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 0 | 4 | 0 | 4 | 0 | 0 |
| 2 | 1 | 0 | 4 | 0 | 4 | 0 | 0 |
| 3 | 2 | 0 | 2 | 0 | 1 | 0 | 0 |
| 4 | 2 | 1 | 4 | 0 | 0 | 0 | 0 |
| 5 | 2 | 0 | 4 | 0 | 0 | 0 | 1 |
| 6 | 3 | 0 | 4 | 0 | 0 | 2 | 0 |
| 7 | 2 | 4 | 0 | 1 | 2 | 0 | 0 |
| 8 | 4 | 0 | 4 | 0 | 4 | 4 | 4 |
| 9 | 2 | 0 | 4 | 0 | 0 | 0 | 0 |
| 10 | 2 | 0 | 3 | 0 | 0 | 0 | 0 |
| 11 | 3 | 1 | 4 | 0 | 4 | 0 | 0 |
| 12 | 4 | 0 | 4 | 0 | 4 | 0 | 0 |
| 13 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| 14 | 2 | 0 | 4 | 0 | 0 | 0 | 1 |
| 15 | 2 | 0 | 4 | 0 | 0 | 2 | 4 |
| 16 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| 17 | 2 | 0 | 4 | 0 | 0 | 0 | 4 |
| 18 | 2 | 2 | 4 | 0 | 1 | 1 | 0 |
| 19 | 2 | 0 | 4 | 0 | 4 | 0 | 0 |
| 20 | 2 | 0 | 4 | 2 | 0 | 0 | 4 |

* All attributes have been graded on a scale of 0 to 4.

TABLE 5.—*Microscopic Changes in Medulla**

| Case | Casts in Loops of Henle | Casts in Collecting Tubules | Interstitial Cells | Edema | Lipidosis |
|---|---|---|---|---|---|
| 1 | 2 | 1 | 0 | 1 | 0 |
| 2 | 2 | 2 | 0 | 1 | 0 |
| 3 | 2 | 0 | 1 | 0 | 0 |
| 4 | 1 | 0 | 0 | 1 | 0 |
| 5 | 0 | 2 | 0 | 0 | 2 |
| 6 | 1 | 4 | 0 | 1 | 0 |
| 7 | 4 | 0 | 0 | 0 | 4 |
| 8 | 4 | 4 | 4 | 2 | 0 |
| 9 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 0 |
| 12 | 4 | 0 | 1 | 2 | 0 |
| 13 | 0 | 0 | 0 | 0 | 0 |
| 14 | 4 | 4 | 0 | 4 | 0 |
| 15 | 4 | 0 | 0 | 0 | 0 |
| 16 | 0 | 2 | 0 | 2 | 0 |
| 17 | 2 | 2 | 4 | 2 | 0 |
| 18 | 2 | 3 | 3 | 1 | 2 |
| 19 | 2 | 0 | 0 | 2 | 0 |
| 20 | 2 | 2 | 4 | 2 | 0 |

* All attributes have been graded on a scale of 0 to 4.

they were present in 19 of the 20 cases, and while not pathognomonic of this disease, they were considered to be comparable in significance to the casts seen in cases of multiple myeloma and other states associated with profound disturbances of protein metabolism. Perhaps all of these are examples of the hyperglobulinosis of Teilum.[30]

30. Teilum, G.: (*a*) Am. J. Path. **24**:389 and (*b*) 409, 1948.

Hyaline casts were present in 2 cases; blood pigment casts (Mallory [31]) in 4; sulfonamide crystals in 6, and bile pigments were associated with the protein casts in 9 cases.

Significant tubular changes were present in the medulla in 16 cases (table 5). Edema was present in 12 cases; interstitial cells were increased in 6; protein, bile and pigment casts were present in the loops of Henle while hyaline casts were found in the collecting tubules in most instances.

*Special Stains.*—In addition to the routine hemalum and eosin preparations examined in all cases, kidney sections prepared with Mallory's Heidenhain azocarmine, Masson's trichrome, Van Gieson's, methyl violet (amyloid), Wilder's reticulum, Wiegert's fibrin and Verhoeff's elastica stains were studied in representative cases. The material that produced the thickening of the glomerular capillary walls was not stained by any of the special technics. Thus it was shown not to be connective tissue hyalin, amyloid or fibrin. It was interpreted as a retrogressive change of the supporting tissue of the capillary network without formation of collagenous fibers.

## COMMENT

Trueta [8] presented clearly the renal physiologic changes in cases of toxic oliguria but did not emphasize the morphologic manifestations. In the present study of cases of toxic oliguria of the type of so-called lower nephron nephrosis, histopathologic changes have been observed in the glomeruli which are similar to those described by Bell [1] in cases of eclampsia. A glomerular lesion seemed to be prerequisite for the oliguria and anuria, since a tubular lesion alone might have been expected to produce polyuria.

Retrogressive changes were found in the glomeruli as well as in the renal tubules in cases of hepatitis and other severe diseases of the liver in which renal damage appeared to be a complication. This association of hepatic and renal changes suggests that with severe hepatic damage the liver fails to deaminize amino acids or other products of protein catabolism which may be toxic to the kidney.

Glomerulonephrosis and protein casts have been noted in patients who had received parenteral amino acids or who had had a profound disturbance of protein metabolism such as is associated with myeloid leukemia and Hodgkin's disease. The protein casts in necrotic tubules occasionally resulted in a foreign body giant cell reaction like that seen in some patients with multiple myeloma. Teilum [20] has stressed the relationship between Boeck's sarcoid, lupus erythematosus and atypical amyloidosis, on the one hand, and hyperglobulinosis associated with a variety of other diseases, including sulfonamide hypersensitivity, multiple myeloma and myeloid leukemia, on the other. This concept offers another possible explanation for the renal changes seen in the present material. Temporary vascular hypertension in cases of hemoglobinuric nephrosis in trau-

31. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938.

matic shock, as reported by Mallory,[25] may have a toxic explanation as appears to be the case for the renal changes in eclampsia. Tubular anoxia is not a suitable explanation, since lipidosis was observed in only 5 cases. In control cases with known slow asphyxial death, tubular lipidosis was an impressive finding. Azotemia was present in 9 of 12 cases in which it was investigated and was not attributable to extrarenal causes or to the usual renal etiologic factors.

The association of jaundice in 11 cases gives a rough index of the importance of hepatic damage in the development of glomerulonephrosis.

SUMMARY

Glomerulonephrosis is presented as the glomerular manifestation of renal ischemia in toxic oliguria or anuria and the so-called lower nephron nephrosis. This renal change is of common occurrence and is found in varying degrees of severity.

Protein casts, gray staining with the hematoxylin and eosin method, are a significant morphologic finding.

The state of the liver is related to this renal condition, and it is suggested that the hyperglobulinosis present in advanced hepatic disease may be a contributing factor.

The reversibility of the changes that occur in the glomeruli and tubules in glomerulonephrosis is attested to by the possibility that some patients may recover from eclampsia as well as from toxic oliguria or anuria.

# CONGENITAL GLYCOGENIC TUMORS OF THE HEART

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TUMORS of the heart having a characteristic microscopic appearance, with large vacuolated cells and glycogen, have been reported under several different names: "congenital glycogenic tumors," "rhabdomyomatosis," "glycogen storage disease," and "nodular glycogenic degeneration of the myocardium." This wide variation of nomenclature reflects the lack of understanding of the cause and the nature of these tumors. The term "rhabdomyoma" has been the most widely used, but it is misleading, since the lesion is probably not a true neoplasm.

The first case was described by von Recklinghausen [1] in 1862. He found several myomas, the largest about the size of a pigeon egg, projecting inside and outside the ventricle of the heart of a newborn infant. The brain was described grossly as having many areas of sclerosis. The first case to be reported in American literature was that contributed by Knox and Schorer [2] in 1906.

There have been three comprehensive reviews of the literature concerning this condition, with listings of the cases: Farber,[3] 1931; Labate,[4] 1939, and Batchelor and Maun [5] 1945. Farber [3] gave an excellent discussion of the theories of the causation of these glycogenic tumors. Since the report of the first case, in 1862, 68 cases have been described in the literature, 5 of which have been reported since the last comprehensive review.[5] Glycogenic tumors of the heart also have been observed in the guinea pig (Hueper [6]), swine (Clausen [7]) and a bovine animal (Pires and Mucciolo [8]).

Following are the 6 newly recorded cases, the listing of which may be considered as a continuation of that of 63 cases by Batchelor and Maun.[5]

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From the Department of Pathology, University of Texas Medical Branch.

1. von Recklinghausen: Monatsschr. f. Geburtsch. u. Frauenkr. **20**:1, 1862.
2. Knox, J. H. M., and Schorer, E. H.: Arch. Pediat. **23**:561, 1906.
3. Farber, S.: Am. J. Path. **7**:105, 1931.
4. Labate, J. S.: Am. J. Path. **15**:137, 1939.
5. Batchelor, T. M., and Maun, M. E.: Arch. Path. **39**:67, 1945.
6. Hueper, W. C.: Am. J. Path. **17**:121, 1941.
7. Clausen, L.: Deutsche tierarztl. Wchnschr. **46**:838, 1938.
8. Pires, E. R., and Mucciolo, P.: Rev. Fac. de med. Vet. Univ. São Paulo, **1**:67, 1939.

Dardinski [9] extracted 2.7 per cent lipids, as well as glycogen, from the tumor tissue in his case and considered the condition to be a combined lipid and glycogen storage disturbance. Haymond and Giordano [10] reported their case as one of glycogen storage disease of the heart and stated that "histologically, glycogen storage disease is characterized by vacuolation of the cardiac muscle fibers and resembles congenital rhabdomyoma of the heart, in which there are also glycogen vacuoles." The distinction made between the two conditions is not clear.

In his original description von Recklinghausen [1] considered the tumor tissue to coincide closely with the sarcoplasm of lower vertebrates, and thought tumors of this type could be considered as localized muscle hyperplasias. Several authors have considered the tumors to arise from Purkinje fibers.[11] Steinbiss,[12] who reported the largest single group

TABLE 1.—*Recently Recorded Cases of the Condition in Question.*

| Case | Author | Sex | Age | Race | Cardiac Tumors | Glycogen | Brain Lesion | Other Abnormalities |
|---|---|---|---|---|---|---|---|---|
| 64 | Haymond and Giordano [10] | F | 5 mo. | W | Single interventricular | Not mentioned | Not mentioned | |
| 65 | Pratt-Thomas [14] | F | 3 days | N | Multiple | Present | Tuberous sclerosis | Dilated tubules of kidney |
| 66 | Leach [14]..... | F | Stillborn | W | Multiple | Not mentioned | Not mentioned | |
| 67 | Dardinski [9]..... | F | 4 days | W | Multiple | Present | Brain not examined | |
| 68 | Hertzog, A. J.: Arch. Path. **47**: 191, 1949 | F | 2 mo. | W | Multiple | None | Brain not examined | |
| 69 | Kidder, L. A.: Arch. Path., this issue | M | Newborn | W | Multiple | Present | Microscopic finding of giant astrocytes | Localized hyperkeratosis of thigh |

of 6 cases, stated that the tumors were often found in hearts where the conduction system was absent. Rehder [13] was the first to consider these tumors as hamartomas. The frequent association of this cardiac lesion with tuberous sclerosis, the presence of glycogen within the tumors and the common coexistence of other anomalies are strong evidence of a congenital metabolic disturbance, the exact nature of which is yet to be determined.

Leach [14] reported the youngest patient, a 6 month fetus weighing only 820 Gm. The oldest patient whose case is recorded was 45 years

9. Dardinski, V. J.: Bull. Georgetown Univ. M. Center **1**:129, 1947.
10. Haymond, J. L., and Giordano, A. S.: Am. J. Clin. Path. **16**:651, 1946.
11. Knox and Schorer.[2] Farber.[3]
12. Steinbiss, W.: Virchows Arch. f. path. Anat. **243**:22, 1923.
13. Rehder, H.: Virchows Arch. f. path. Anat. **217**:174, 1914.
14. Leach, W. B.: Arch. Path. **44**:198, 1947.

of age (Lymburner [15]). Figure 1 shows the age incidence of patients with glycogenic tumors of the heart and the incidence of tuberous sclerosis in each age group. Almost 40 per cent of the patients were dead at 6 months of age, 60 per cent by the age of 1 year, and 80 per cent by the age of 5 years. The ages of 2 patients were not given. It is interesting to note the low percentage of the patients 6 months of age or younger with the diagnosis of tuberous sclerosis as compared with the higher percentage of the older age groups with such a diagnosis. Part of this may be acounted for because of failure to examine the brain in some cases. In other cases the cerebral lesion may have been so small in the newborn as to be missed grossly, whereas in the older

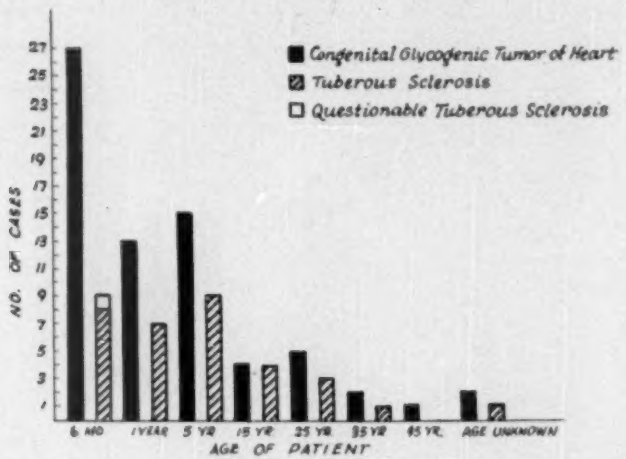


Fig. 1.—Association of glycogenic tumors of the heart and tuberous sclerosis.

patients it could be picked up more readily, since this is a progressive disease process. In the case being reported no gross abnormalities of the brain were seen; however, after examination of numerous sections, one area was found compatible with, but not pathognomonic of, tuberous sclerosis.

The sex of the patient was given in only 40 of the 69 cases; in 60 per cent of these the patient was a male and in 40 per cent a female. Only 1 Negro, an infant, was found in the group.[16] There has been no special site in the heart for occurrence of glycogenic tumors; they

15. Lymburner, R. M.: Canad. M. A. J. **30**:368, 1934.

16. Pratt-Thomas, H. R.: Am. J. Path. **23**:189, 1947.

have involved practically all portions. In 53 of the cases the heart showed multiple tumors, in 12 single tumors, while in 3 cases a diffuse involvement of the cardiac muscle was found. One case was diagnosed by photograph only (Tamura [17]).

The frequency and the site of the lesions associated with glycogenic tumors of the heart are shown in table 1. These data show that tuberous sclerosis is the most frequent associated lesion, with renal lesions second.

Batchelor and Maun [5] stated that clinical symptoms were rare except in patients with tumors situated on the valve leaflets; there the tumors produced a local murmur. Cyanosis was found to be a frequent symptom in patients who died suddenly. The patients with tuberous sclerosis

TABLE 2.—*Frequency and Site of Lesions Associated with Congenital Glycogenic Tumors of the Heart.*

| Organ | Lesion | Cases | |
|---|---|---|---|
| Brain | Tuberous sclerosis | 33 | 1 questionable |
| | Multiple neuroglioma | 1 | |
| | Spongioblastoma | 2 | |
| Kidney * | Tumors | 15 | |
| | Cysts | 12 | |
| | Anomalies | 3 | |
| Liver | Hepatomegaly | 5 | |
| | Angiomyolipoma | 1 | |
| Skin | Tumors | 5 | |
| | Localized hyperkeratosis | 1 | |
| Spleen | Splenomegaly | 2 | |
| Lung | Tumor | 1 | |
| | Anomaly | 1 | |
| Breast | Tumor | 1 | |
| Heart | Anomaly | 1 | |
| Pancreas | Anomaly | 1 | |
| Esophagus | Anomaly | 1 | |
| Rectum | Anomaly | 1 | |
| Pylorus | Stenosis | 1 | |
| Lip | Harelip | 1 | |

* Several of the kidneys contained both cysts and tumors.

showed neurologic symptoms, such as delayed ability to walk, retarded mental development, delayed speech, indifference to surroundings and epileptiform attacks.

The following is the sixty-ninth case of glycogenic tumors of the heart to be reported. It is of interest because of the rarity of this disease.

### REPORT OF A CASE

The patient was a full term white male infant. At the time of delivery a loop of umbilical cord had prolapsed. No pulse was present in the cord. Immediately following delivery, a faint heart sound was heard, but this soon ceased. The infant was quite flaccid immediately after delivery and did not respond to any stimuli.

17. Tamura, O.: Gann **30**:391, 1936.

Two years previously, at the age of 33, the mother had delivered her first child, a premature, stillborn infant, after premature separation of the placenta. An autopsy revealed no abnormalities in that infant. Approximately eleven months after the first delivery, a full term infant was born, which is alive and well at the present time, with no apparent abnormalities. The present infant represented her third pregnancy. The Rh factor of the parents was not determined.

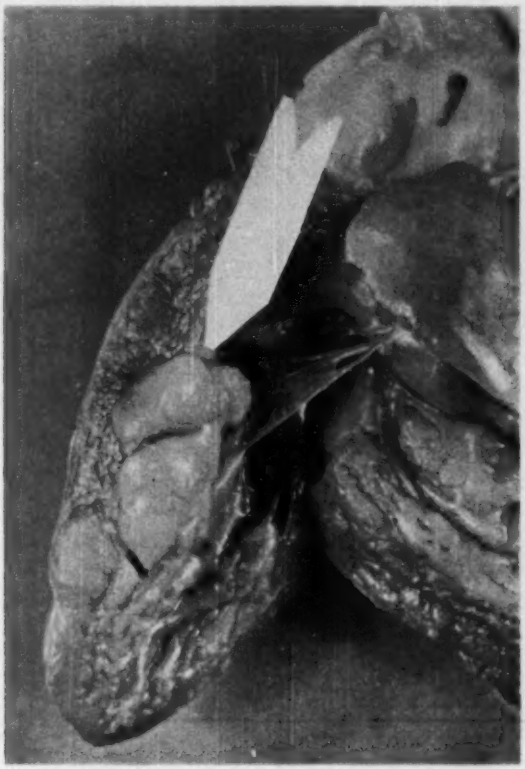

Fig. 2.—Glycogenic tumors involving the papillary muscles and the wall of the right ventricle of the heart.

*Postmortem Examination.*—The body was that of a well developed white male infant weighing 4,480 Gm. and measuring 55 cm. from crown to heel. The autopsy was performed ten days after death, during which time the body was well refrigerated. On external examination the only abnormalities found were three slightly elevated flat nodules on the lateral aspect of the right thigh. These were round and of the same color as the adjacent skin. Microscopic examination of these nodules showed only localized areas of hyperkeratosis.

The heart weighed 35 Gm. The epicardium was glistening, but four slightly elevated nodules were seen near the apex of the wall of the right ventricle and on the anterior portion of the septum. These nodules averaged 5 mm. in diameter. They were light yellowish pink. On sectioning the heart, one saw another tumor mass, measuring 1 cm. in diameter, involving the papillary muscles in the right ventricle. A nodule measuring 7 mm. in diameter was found high in the septum. All of the tumor nodules appeared well circumscribed, although not encapsulated. They were slightly firmer in consistency and lighter in color than the surrounding cardiac muscle. The coronary vessels, the valves and the myocardium showed no other abnormalities.

Some blocks from the heart, after being fixed in a modified Zenker's solution for fourteen hours, were placed in absolute alcohol. Histologic sections were stained with Best's carmine, hematoxylin and phloxine, Masson's trichrome, Mallory's phosphotungstic acid-hematoxylin and azocarmine technics, and sudan

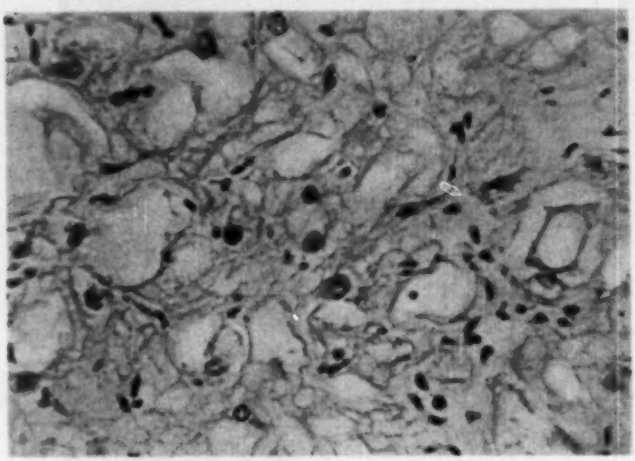

Fig. 3.—Glycogenic tumor. Note the large vacuoles in the cytoplasm and the reticular arrangement of the processes. Hematoxylin and phloxine; × 500.

III. The sections from all the different tumor nodules showed the same histologic changes. There was a distinct line of demarcation between tumor tissue and the adjacent myocardium without any definite evidence of a capsule. The general framework of the tumor was a coarse reticular network of cytoplasmic processes showing distinct cross striations and many large, irregular vacuoles of varying size, with finely granular pink cytoplasm around many of the vacuoles. In the cytoplasm adjacent to the large vacuoles were a moderate number of large, pale, vacuolated, round to oval-shaped uniform-sized nuclei. Many of these cells with large vacuoles and cytoplasmic processes had the characteristic appearance of the so-called "spider cells" described by Cesares-Demel.[18] Cellular outlines were indistinct, and there was no evidence of mitotic activity.

18. Cesares-Demel, A.: Arch. per le sc. med. **19**:139, 1895.

Best's carmine stain showed some fine pink granular glycogen in the cytoplasm of the tumor cells. Stains for fat were negative. A very slight amount of connective tissue was seen around the small blood vessels and in some areas around

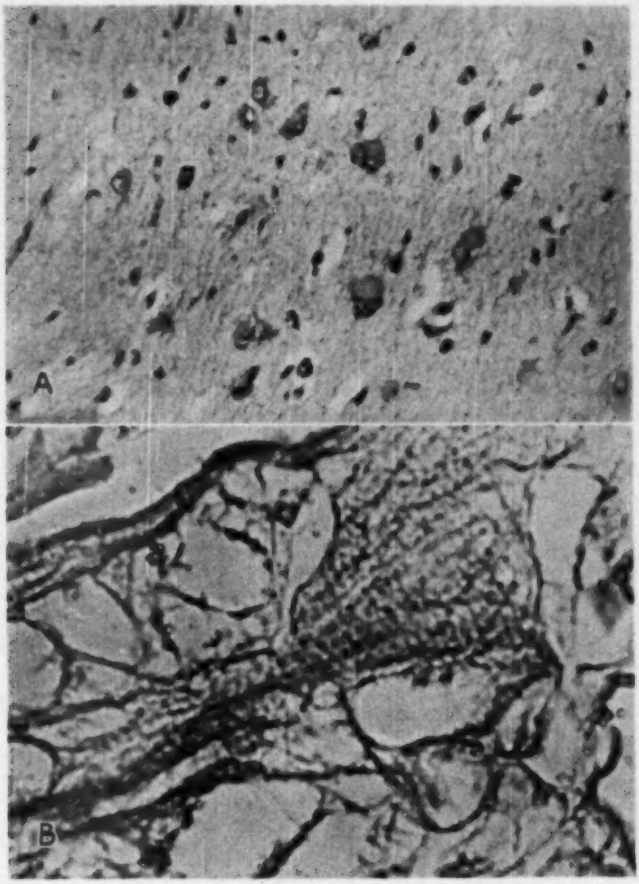


Fig. 4.—*A*, an area of giant astrocytes in the brain. Several of these astrocytes contain two nuclei. Hematoxylin and phloxine; × 50.

*B*, glycogenic tumor. Cross striations are shown in the cytoplasm of the tumor cells. Mallory's phosphotungstic acid-hematoxylin; × 1144.

the periphery of the tumor. This stained blue with Mallory's technic, while the cytoplasm and cytoplasmic processes of the cells stained red. Masson's stain

showed a similar picture, with the tumor tissue staining the same as the muscle fibers of the myocardium. Distinct cross striations were seen.

The brain and spinal cord and both eyes were removed. Moderate congestion of the vessels of the meninges was present. The brain weighed 510 Gm., and the surface showed the usual convolutional pattern. No gross abnormalities were noted in the brain, either on the cortical surface or in multiple sections. Sections of the spinal cord at each level showed a normal configuration. The eyes showed no abnormalities either grossly or microscopically.

Many microscopic sections of cerebral cortex, basal ganglions, pons, medulla, cerebellum and spinal cord were examined. One localized area composed of giant astrocytes having abundant homogeneous pink-staining cytoplasm and containing one or two eccentrically located oval nuclei was found beneath the cortex. Both the brain and the cord showed moderate autolytic changes.

The viscera were carefully examined but showed no significant lesions. The lungs weighed 80 Gm. and were atelectatic. The liver weighed 240 Gm., the spleen 16 Gm., and the kidneys 36 Gm. each. Some congestion and petechiae were found in the gastrointestinal tract.

## SUMMARY

A case of multiple congenital glycogenic tumors of the heart of a newborn infant is reported, in which glycogen was demonstrated and cross striations were seen within the cells. An area of giant astrocytes compatible with, but not pathognomonic of, tuberous sclerosis was observed in the brain.

The literature on glycogenic tumors of the heart has been reviewed; a total of 69 cases have now been reported.

The associated incidence of tuberous sclerosis is probably much greater than reported in the literature, because the central nervous system was not examined in a number of the cases and the lowest percentage of reported incidence is in infants 6 months of age or younger, a group in which the lesion is probably frequently missed.

The causation of these glycogenic tumors remains obscure, although it is probably related to a glycogen storage disturbance.

# DIFFUSE GRANULOMATOUS AORTITIS WITH GIANT CELLS

## Associated with Partial Rupture and Dissection of the Aorta

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EXAMPLES of idiopathic granulomatous aortitis with giant cell formation are distinctly rare. The case to be reported is offered as an addition to those described in the brief literature, and is the only one in which this disease was associated with partial rupture and limited dissection of the aorta.

### REPORT OF A CASE

A 58 year old white man was admitted to the Royal Victoria Hospital in Montreal, Canada, suffering from paralysis and numbness of the left arm and weakness of the left leg. These symptoms had been present for one day, and their onset had been sudden, having caused the patient to fall to the floor, although he had not lost consciousness.

Inquiry revealed that he had been admitted to a hospital two years previously for a condition diagnosed as a hemorrhage of the left lobe of the cerebellum. He was found to have vascular hypertension at that time. For the past six months prior to the present admission he had suffered from mild ataxia, and for the previous one month had been conscious of increasing difficulty in executing movements with the left arm. Further inquiry regarding his history produced essentially irrelative information.

The temperature and the pulse and respiratory rates were normal. The blood pressure was 210 systolic and 100 diastolic. The diagnosis was cerebral hemorrhage on the right side. The Wassermann test of the blood was negative. The patient died eight days after admission while in a semicomatose condition and with the signs of bronchopneumonia.

*Autopsy.*—A complete autopsy was made eight hours after death. The body was that of a large, obese man. There was terminal bronchopneumonia. At the apex of the left lung there was a minute fibrous scar.

The heart weighed 610 Gm., and there was hypertrophy of the left ventricle. In the myocardium there were some fatty areas. The aorta was moderately sclerotic, the sclerosis being most severe in the abdominal portion. It showed a longitudinal, irregular, partially healed tear of the intima extending up from the edge of the left posterior sinus of Valsalva (fig. 1), measuring 3.5 by 0.7 by 0.1 cm. The tear did not extend through the full thickness of the wall. The right internal carotid artery, close to the circle of Willis, contained a thrombus, and blood lay between the media and the adventitia of the vessel. The right middle cerebral artery was also thrombosed. The entire right half of the cerebrum was swollen

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and soft, while the basal ganglions and the internal capsule were frankly necrotic. No gross hemorrhages were seen in the brain, but there were a few petechiae in the right frontal lobe. A minute gray area of softening was present in the left side of the pons.

*Microscopic Examination.*—The thyroid gland, heart, lungs, liver, spleen, pancreas, prostate, adrenal glands and pituitary gland showed no relevant abnormalities and presented only slight arteriosclerotic changes. The kidneys were relatively free from vascular lesions. The brain presented recent infarction, while the right internal carotid artery, close to the circle of Willis, was occluded by a recent thrombus. The wall of this vessel was considerably thickened by intimal sclerosis, and the sclerosed portion was rich in crystal clefts and calcium deposits. The

Fig. 1.—Photograph of the root of the aorta showing an irregular partial rupture and dissection of the organ in the ascending arch. A block has been removed from the area of the rupture.

media was irregularly thinned and had a large recent hemorrhage within it. This hemorrhage involved about one eighth of the circumference of the artery, and encroached on its adventitia. In the adventitia the vasa vasorum were hyperemic; diffuse minor hemorrhage was present in it, and many polymorphonuclear and small and large mononuclear cells were seen throughout the connective tissue.

The most interesting changes were found in the aorta and the left common iliac artery. The various regions of the aorta showed similar intimal sclerosis and destruction of the media, and a granulomatous reaction with giant cell formation in the area of medial destruction, as well as vascularization of and hemorrhage into the medial lesions, and a cellular infiltration of the adventitia in which plasma cells, lymphocytes and mononuclear cells participated.

The sclerotic changes in the intima appeared to be independent of the other changes in the aorta, and differed in no respect whatever from those observed in the aortas of a group of patients of corresponding age. These changes were graded arbitrarily as moderate in the ascending portion of the arch and in the area of incomplete rupture, marked in the transverse and descending portions of the arch and severe in the abdominal aorta and iliac arteries.

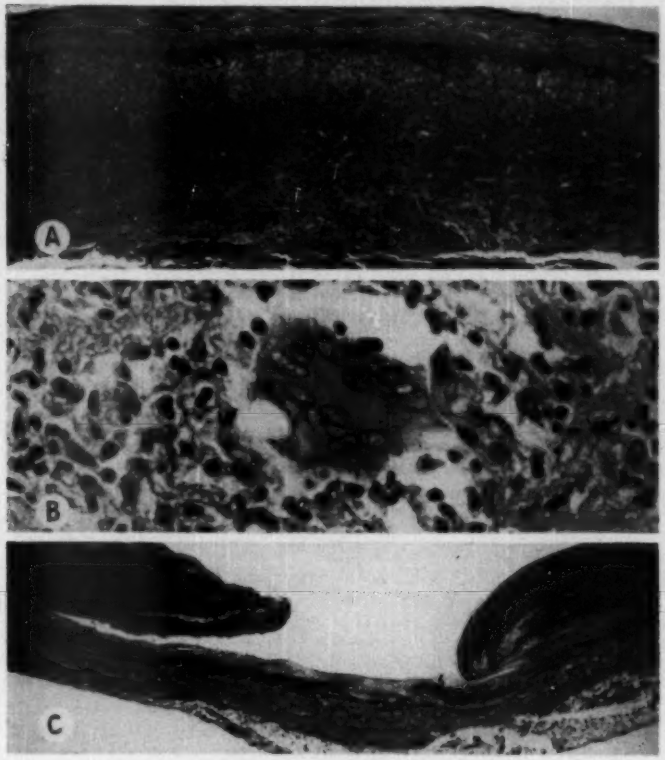


Fig. 2.—*A*, photomicrograph of an area of granulomatous reaction in the descending portion of the aortic arch. Masson's trichrome stain; × 25.
*B*, photomicrograph of the granulomatous reaction with a giant cell. Hematoxylin and eosin; × 500.
*C*, photomicrograph of the partial rupture and incomplete dissection of the ascending portion of the arch. Note the marked destruction of elastica. Elastic and connective tissue stain; × 10.

The changes affecting the media involved about one third of its thickness in the ascending portion of the arch at the junction of the middle and outer thirds. In the transverse and descending portions the changes involved the inner two thirds of the media (fig. 2*A*). The upper abdominal region of the aorta showed moder-

ate alterations in the inner one third, while the lower abdominal region showed severe changes in the inner two thirds of the media. The media of the left common iliac artery contained one small area of similar change in its outer third. In addition, the entire thickness of the media, exclusive of the zones described, showed mild fatty degeneration when stained with scarlet red.

Among the changes in the media was an almost complete loss of muscle fibers, although in the least involved areas a few isolated fibers and their nuclei could be detected with Masson's trichrome stain, Van Gieson's stain or phosphotungstic acid–hematoxylin. Similarly, the elastic tissue was severely affected, and in some areas extending over several low power fields no elastic fibers could be found by either the Verhoeff or the Weigert method. Elastic fiber fragments, disorientated, swollen, beaded, comminuted and frayed, could be found in and at the edges of the lesions, while the elastic fibers outside the affected areas showed only straightening, parallelism and minor degenerative changes. Alterations of the collagen fibers were also striking. The usual precise structure of the fibrillar collagenous elements was totally disrupted so that it became a tangled and fragmented reticular maze. The fibrillar character of the collagen was often lost, and in many areas the network appeared swollen and amorphous. While its staining reactions were preserved in general, about 5 per cent of the collagen in any given field showed the chromatic changes which are interpreted as indicating degeneration or necrosis, staining faintly red with Masson's trichrome and yellow with Van Gieson's stain.

In the interstices of the collagen network was a cellular infiltration that varied in amount from section to section, although its character was relatively constant. In general, the degree of cellular reaction varied directly with the severity of the necrotic and degenerative changes. It was usually diffuse, but rarely was aggregated into ill defined foci. More than one half of the cells were plasma cells, often abnormal in nature and large in size. The remainder of the cells comprised about equal proportions of large mononuclear cells, lymphocytes and cells that appeared to be intermediate forms between lymphocytes and plasma cells. Degenerating plasma cells, some showing Russell's bodies, were seen in moderate numbers. Fibroblasts, fibrocytes and polymorphonuclear leukocytes were rare. Moderate numbers of cells of undetermined type showing extremely severe karyolytic changes were noted throughout. Occasionally, small but definite cellular foci were seen, and these usually contained a majority of lymphocytes with fewer plasma cells. Multinucleated giant cells, typical of both the Langhans and the common foreign body type, were found in all sections of the aorta, but they were not numerous (fig. 2*B*). Small multinucleated giant cells of the foreign body type predominated.

The affected areas were richly vascularized, particularly toward their adventitial side, and these capillary and sinusoidal channels were dilated and full of red blood cells. Small extravasations of blood were observed throughout.

The adventitia appeared thickened, owing to separation of its fibers. Many dilated and engorged blood channels were visible, while scattered focal and diffuse collections of lymphocytes and plasma cells in moderate numbers were present.

Sections through the area of the intimal tear showed an incomplete rupture and dissection with marked degenerative and inflammatory changes similar to those described and extending through almost the entire thickness of the media (fig. 2*C*). This altered tissue formed the base and angles of the small defect. The lips of the partial perforation were rounded and contained a few imperfect elastic fibers. They were undercut by a lateral dissection which had extended for

a millimeter or two on either side. The usual granulomatous reaction with formation of giant cells was present in this area, but not in its most severe form. No granulation tissue was present.

Gram-positive, gram-negative and acid-fast bacteria could not be found in the many sections specially stained to demonstrate their presence. Nor were treponemes found in a block treated by the Levaditi method.

## COMMENT

A disease of the aorta that is morphologically similar to that described was reported by Sproul and Hawthorne,[1] in 1937, as unique chronic diffuse mesaortitis. The condition was again described in 1941, by Gilmour,[2] who designated it as giant cell chronic arteritis. No other comparable reports appear in the literature, although certain authors[3] have described conditions that may possibly represent the same lesion.

As first described by Sproul and Hawthorne[1] in 2 cases the condition was clinically silent and caused no significant gross changes in the aorta. On microscopic examination there were degeneration of the musculocollagenous elements of the middle third of the media, without scar formation, and a heavy diffuse lymphocytic and plasma cell infiltration of the affected area. A sparse number of giant cells of the foreign body type were present in the cellular reaction. The authors reviewed the relevant literature and concluded that they had found a lesion that had not been previously described. They also suggested that it might have an allergic cause. Gilmour[2] reported 4 cases of giant cell chronic arteritis. The findings were essentially similar to those of Sproul and Hawthorne[1] except that an involvement of large branch vessels was noted and a few further histologic observations were added to those of the original report. Gilmour expressed the opinion that the lesion was a definite entity of idiopathic nature comparable in many respects to the lesions of temporal arteritis.

The case described here differs in only minor particulars from those already recorded in the literature. The most common cell in the inflammatory reaction of this case was a large plasma cell, and, where the reaction was severe, there was a marked and proportionate destruction of muscular, elastic and, to a lesser extent, collagenous elements, a degree of destruction that is not described by the other authors.

The possibility that this lesion may be a variant of some commoner form of arteritis exists. In my opinion, only acute syphilitic aortitis, periarteritis nodosa and temporal arteritis are worthy of serious consideration in this respect.

1. Sproul, E. E., and Hawthorne, J. J.: Am. J. Path. **13**:311, 1937.

2. Gilmour, J. R.: J. Path. & Bact. **53**:263, 1941.

3. (*a*) Barnard, W. E.: J. Path. & Bact. **40**:433, 1935. (*b*) Chasnoff, J., and Vorzimer, J. J.: Ann. Int. Med. **20**:327, 1944. (*c*) Harbitz, F.: Arch. Path. **1**:499, 1926.

Clinically the patient was free from syphilis, and pathologically the findings did not suggest chronic syphilitic aortitis in either distribution or in gross or microscopic appearance. Moreover, the lesion lacked the distribution, the focal coagulative, gummy necrosis and the moderate polymorphonuclear cell infiltration found in acute syphilitic mesaortitis. Treponemes were not demonstrated by the Levaditi method. Indeed, the only reason to consider syphilis as an etiologic factor of this lesion was the presence of an area of granulomatous aortitis rich in plasma cells.

Periarteritis nodosa is not known to affect the large elastic arteries, although Wolff [4] reported a case involving the vasa vasorum of the aorta. The destruction of the medial elements of the vessel wall is suggestive of periarteritis, but it was diffuse rather than focal. The cellular reaction in which plasma cell elements predominated was not consistent with the usual picture of periarteritis nodosa, and, moreover, the disease was not found in other organs and vessels of the body.

On the other hand, the lesion bears a considerable resemblance to those described in temporal arteritis, differing chiefly in the fact that polymorphonuclear cells were extremely rare and in the fact that the entire vessel was diffusely involved. Neither of these differences appears to present a serious obstacle to a comparison of the two diseases. It has been suggested that temporal arteritis is merely a striking symptom of generalized arteritis,[5] but whether this arteritis can occur without coincident involvement of the temporal artery is not known.

The lesion is not considered compatible, either clinically or pathologically, with a diagnosis of tuberculous aortitis [6] or, in spite of the presence of a dissecting aneurysm, with a diagnosis of medionecrosis aortae idiopathica cystica.[7] The presence of a partial rupture and dissection of the aorta is an added feature of interest in the present case. It provides an example of a dissecting aneurysm of the aorta that was based on a lesion other than the medionecrosis described by Erdheim. At the same time it is noted that its location and gross appearance were typical of such dissecting aneurysms and that it occurred in a patient who had vascular hypertension. Gilmour [2] reported the rupture of an aneurysm of the right subclavian artery in one of his cases of chronic giant cell arteritis. The disease must, therefore, be considered as one that predisposes to arterial rupture.

4. Wolff, K. W.: Virchows Arch. f. path. Anat. **297**:177, 1936.

5. Cooke, W. T.; Cloake, P. C. P.; Govan, A. D. T., and Colbeck, J. C.: Quart. J. Med. **15**:47, 1946. Temporal Arteritis, editorial, J. A. M. A. **131**:669, 1946. Gilmour.[2] Chasnoff and Vorzimer.[3b]

6. Jores, L., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924. Barnard.[3a]

7. Erdheim, J.: Virchows Arch. f. path. Anat. **276**:187, 1930. Shennan, T.: M. Research Council (Spec. Report Series no. 193) 1934, p. 1.

Harbitz [20] described his case of bilateral carotid arteritis as follows: "From the anatomic point of view, there was an arteritis of the aorta, and of some of its principal branches, particularly the carotids, with secondary thrombosis." A similar description can be employed in the present case. However, while it is probable that the arteritis of the carotid artery and that of the aorta were similar in nature, it is not certain. Two of Gilmour's [8] cases of giant cell chronic arteritis also showed thrombosis of the internal carotid arteries. This association of chronic arteritis of the aorta and carotid arteries and thrombosis of the latter is noteworthy. It is sufficiently striking to compel a careful examination of the aorta in every case in which thrombosis of one or both carotid arteries occurs without obvious cause. Indeed, in the cases so far reported, diffuse granulomatous giant cell arteritis commonly affected the internal carotid and other arteries in addition to the aorta. Similarly, in association with temporal arteritis, involvement of arteries other than the temporal branches of the external carotid artery is not uncommon. Accordingly, it seems justifiable in view of the histologic similarity of all these lesions to suggest the possibility that all of them represent manifestations of a vascular inflammatory disease that may be widespread in the aorta and its branches or that may be localized in particular arteries, among which the temporal arteries and the carotid arteries appear to be particularly vulnerable.

## SUMMARY

A case of diffuse granulomatous giant cell aortitis of unknown cause is presented. It is the seventh such case reported in the literature. Associated with the lesion were partial rupture and dissection of the aorta, thrombotic occlusion of the right internal carotid artery and massive infarction of the right half of the cerebrum.

# ADENOMATOID CHANGES OF RENAL GLOMERULAR CAPSULAR EPITHELIUM ASSOCIATED WITH ADRENAL TUMOR

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ADENOMATOID changes of renal glomerular capsular epithelium associated with a carcinoma of the gallbladder have been reported by Eisen.[1] Somewhat similar changes have been reported in animals. In 1946 a patient with the peculiar changes in the capsular epithelium came to our attention, the findings being of sufficient interest to report the case briefly.

## REPORT OF A CASE

A 16 year old Negro boy was admitted to Memorial Hospital in Houston complaining of shortness of breath and enlargement of the abdomen. The enlargement of the abdomen had been present for five months, and during this five month period his weight had decreased 38 pounds (17 Kg.). On admission he was dehydrated and emaciated, with a blood pressure of 110 systolic and 70 diastolic. The main finding was a greatly enlarged abdomen, symmetric and rather globular. The consistency was so firm it was impossible to determine by palpation the cause of the enlargement. However, one examiner thought that there was a large tumor of the right kidney. The veins of the abdominal wall were greatly distended.

The hemoglobin was 7 Gm. per hundred cubic centimeters; the erythrocyte count, 2,280,000 per cubic millimeter; the total white cell count, 6,800 per cubic millimeter, with polymorphonuclear neutrophils 73, lymphocytes 22, eosinophils 5 and nucleated red blood cells 2 per hundred white cells counted. The urine was normal.

Laparotomy disclosed an enlarged liver containing several large masses varying from 5 to 15 cm. in diameter. These had liquefied centers. Some of these were drained of necrotic liquid material in order to give symptomatic relief. No further exploration was done, on account of the poor condition of the patient. He died two days later.

At postmortem examination there was about 2,000 cc. of bloody fluid under pressure in the abdomen. The liver was enlarged and adherent to diaphragm and anterior abdominal wall. It contained many tumors, which were soft and pink, the larger ones having liquefied centers. On the right a large retroperitoneal mass, measuring 28 by 17 by 17 cm., completely replaced the adrenal gland. It

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1. Eisen, H. N.: Am. J. Path. **22**:597-600, 1946.

pushed the right kidney downward and displaced the liver forward and upward. There was a small metastatic nodule, 0.5 cm. in diameter, just under the pleura on the diaphragmatic surface of the right lung.

Since the main mass appeared to arise from the right adrenal gland, most of the interest centered on it. This mass was quite firm, with a pink cut surface, showing a few small areas of necrosis. Microscopic examination revealed closely packed small oval cells with a moderate amount of pink-staining cytoplasm and deeply staining nuclei. The major portion of the tissue showed no definite arrangement. In places a suggestion of papillary adenocarcinoma was in evidence, but on the whole there was no definite pattern. Rosettes and pseudorosettes were not seen. A small to moderate amount of fibrous connective tissue stroma was present in the main tumor. The metastatic masses in the liver (fig. 1) and in

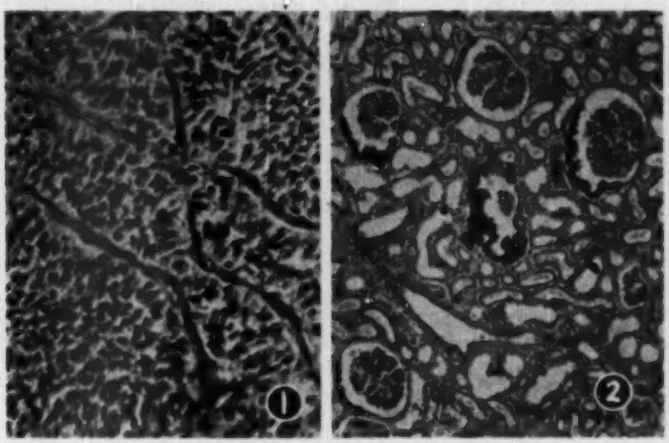


Fig. 1.—Photomicrograph illustrating the metastases observed in the liver. The primary tumor in the adrenal gland had a similar structure but was more fibrous.

Fig. 2.—Photomicrograph of a kidney section showing the tumor cells lining Bowman's capsules.

the subpleural region revealed similar cells, although much necrosis had occurred in those in the liver. There was less fibrous stroma in the hepatic masses.

Microscopic examination of the kidneys revealed a surprising appearance (fig. 2). Many of Bowman's capsules were lined by rather tall columnar cells, forming a single layer. These had deeply staining nuclei and lightly staining cytoplasm and in many respects resembled the cells of the main tumor, in the adrenal gland, and those of the metastases.

Not all glomeruli were involved, about 25 to 50 per cent escaping. Also, in some of the involved tufts the capsule was only partially lined by these peculiar neoplastic cells. At times there were so many of these peculiar cells that papillary formations projected into the capsular spaces. Occasionally the neoplastic cells extended a short distance into the proximal convoluted tubules.

## COMMENT

The tumor of the adrenal gland was apparently the primary neoplasm and was either an atypical neuroblastoma or an uncommon adenocarcinoma of the adrenal gland. The hepatic masses and the solitary subpleural nodule were unquestionably of the same type of tumor tissue, and were metastases.

The consensus was that the tumor was a neuroblastoma arising in the adrenal medulla, even though it lacked definite rosette arrangement and in spite of the age of the patient (16 years), most of such tumors occurring in infancy and early childhood.

The peculiar cells lining the capsules of the glomerular tufts may or may not have been of tumor nature. Microscopically they seemed to resemble those of the adrenal tumor. It is difficult to explain them on a metastatic basis, however, since no actual neoplastic masses were found in the kidneys. Microscopically there were no tumor cells in the glomerular tufts and one could reason that if the peculiar capsular cells were tumor cells, there should be evidence of tumor cells in the glomerular tufts—presuming, of course, that such cells were blood-borne to the kidneys in some circuitous manner. These cells resembled those in the illustrations of Eisen's [1] report. In his case the primary tumor was adenocarcinoma of the gallbladder, with little resemblance of cell types.

The changes in the kidneys produced no changes in the urine. One can postulate that these peculiar lining cells were neoplastic and probably metastatic; or that they were not of tumor nature but were metaplastic cells present in the kidneys because of unknown causes. Since the only other reported instance also concerned a patient dying of a cancer, the metaplasia may in some unknown way be brought about indirectly by cancer. The strongest argument against this is that it does not occur in a large number of patients dying of neoplasms of all sorts, including those of the adrenal glands.

In order to prove definitely that the renal change is primary it is necessary to find a patient having this change with no cancer elsewhere in the body.

## SUMMARY

Peculiar epithelial cells were found lining Bowman's capsule in a case of tumor of the adrenal gland. They resembled those observed by Eisen [1] in a case of carcinoma of the gallbladder. Their true nature is unknown.

# General Reviews

## CHORIOCARCINOMA

### A General Review, with an Analysis of Five Hundred and Sixteen Cases

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WE HAVE analyzed the data and material available to us concerning 23 patients who were at one time or another considered as certainly or probably having choriocarcinoma. We have also read the relevant literature available to us, which contains reports of 493 cases. Included in this figure are the 189 cases annotated by Teacher.[1] Except in a few instances we have not read the original reports from which Teacher's annotations were taken. Many of the cases in our series are, of course, included in the series published by Pollosson and Violet,[2] 455 cases, and by von Szathmáry,[3] 500 cases.

### INCIDENCE OF CHORIOCARCINOMA

#### ABSOLUTE INCIDENCE

The literature can give only a minimum estimate of this, as of that of any disease. The conditions which precede it are common—even hydatidiform mole is not rare—whereas choriocarcinoma is an extremely rare disease. Figures for its absolute incidence vary greatly, but one of the best controlled estimates is that given by Schumann and Voegelin.[4] Their figures were taken from a strictly defined area (the corporate limits of Philadelphia) over a five year period. They calculated that the incidence of choriocarcinoma was 1:13,850 pregnancies (0.007) per cent). (Of the 15 cases of choriocarcinoma which occurred, 8 were fatal as a direct result of the neoplasm, giving for fatal cases an incidence of 1:26,000 [0.004 per cent]).

An analysis of 497 cases is shown in table 1.

From the Royal College of Physicians' Laboratory.

1. Teacher, J. H.: J. Obst. & Gynaec. Brit. Emp. **4**:1 and 145, 1903.
2. Pollosson, A., and Violet, H.: Ann. de gynéc. et d'obst. **70**:257, 1913.
3. Von Szathmáry, Z.: Ztschr. f. Geburtsh. u. Gynäk. **98**:444, 1930.
4. Schumann, E. A., and Voegelin, A. W.: Am. J. Obst. & Gynec. **33**:473, 1937.

Six months was chosen as the follow-up period for two reasons: 1. Practically all the patients who died directly of the disease died within six months after operation. 2. The literature does not afford many examples of a follow-up longer than this.

Every case claimed by an author to be one of choriocarcinoma has been accepted as such if there was abnormal trophoblastic proliferation—although a cancerous change might be doubtful. Most of the cases not accepted seemed to be cases of ovarian carcinoma. There was also a group of 19 cases not included in this table: 4 of primary nongestational choriocarcinoma (of the liver in 2, of the jejunum in 1, of the ovary in 1); 1 case in which the patient was a virgin of 71 years; 14 cases insufficiently described for analysis.

TABLE 1.—*An Analysis of 497 Cases of Choriocarcinoma Following Different Types of Pregnancy from the Standpoint of the Outcome*

| | Full Term Pregnancy | Abortion | Hydatidiform Mole | Tubal Pregnancy | Type Not Known | Total |
|---|---|---|---|---|---|---|
| Cases in which death was directly attributed to choriocarcinoma | 60 | 60 | 57 | 12 | 9 | 198 |
| Cases in which patient survived for at least 6 mo. after treatment with apparent cure | 22 | 82 | 139 | 6 | 1 | 250 |
| Cases of demonstrated curability, rate per cent | 27 | 46 | 71 | 33 | .. | 53 |
| Cases in which no follow-up data were given | 2 | 4 | 15 | 2 | .. | 23 |
| Cases in which patient died postoperatively or as a result of effects not directly attributable to choriocarcinoma | 5 | 20 | 16 | 1 | .. | 42 |
| Total number of cases | 89 | 186 | 227 | 21 | 10 | 483 |
| Cases not acceptable as cases of choriocarcinoma | | | | | | 14 |

INCIDENCE BY AGE

In order to compare the frequency of choriocarcinoma with that of maternity at different ages, the following procedure was carried out:

1. The frequency of choriocarcinoma—(*a*) fatal cases only, (*b*) total number of cases diagnosed—was noted for each five year age group in this series.

2. The number of cases of maternity in England and Wales in 1939 was found from the Registrar General's tables.[5] It is obvious that such figures applying to a single year only must be qualified by reference to the changes occurring in the age incidence of maternity over the decades and in the different countries covered by our series; and this series itself is, of course, subject to all kinds of more or less recognizable selectivity.

3. The proportionate frequency of choriocarcinoma per thousand cases of maternity in each age group was found by dividing the figure recorded for each age group in step 1 by the corresponding figure recorded in step 2 and multiplying the result by 1,000.

5. Registrar-General's Statistical Review of England and Wales for the Year 1939 (New Annual Series, no. 19), London, His Majesty's Stationery Office, 1944, pt. 2, table AA, p. 92 and table 25, p. 102.

The results obtained are given in table 2 (the factor $x$ is added to indicate that these proportions are not absolute but valid only in relation to each other).

It is striking that the age frequency of choriocarcinoma per thousand cases of maternity runs almost precisely parallel to the age incidence of carcinoma in the general population.

## RELATIVE FREQUENCY WITH WHICH CHORIOCARCINOMA HAS BEEN PRECEDED BY DIFFERENT TYPES OF PREGNANCY

It is obvious that the threshold of publication for a case of tubal choriocarcinoma is much lower than that for the intrauterine variety

TABLE 2.—*Proportionate Frequency of Choriocarcinoma Considered in Relation to Number of Cases of Maternity*

| Age Group | Fatal Choriocarcinoma | Diagnosed Choriocarcinoma |
|---|---|---|
| 0-19 | 0.10x | 0.55x |
| 20-24 | 0.18x | 0.48x |
| 25-29 | 0.25x | 0.45x |
| 30-34 | 0.24x | 0.61x |
| 35-39 | 0.44x | 0.89x |
| 40-44 | 0.68x | 2.32x |
| 45-49 | 0.42x | 18.80x |

TABLE 3.—*Relative Frequency with Which Uterine Choriocarcinoma Followed Different Types of Pregnancy*

| | Lethal Cases of Uterine Choriocarcinoma, per Cent | All Cases in Which Uterine Choriocarcinoma Was Diagnosed, per Cent |
|---|---|---|
| After normal pregnancy | 34 | 20 |
| After abortion | 34 | 30 |
| After hydatidiform mole | 32 | 50 |

and that the reported frequency of the tubal form is not comparable with that of the uterine. The relative frequency with which uterine choriocarcinoma was preceded by different types of pregnancy in this series is given in table 3.

The difference in the frequencies between fatal choriocarcinoma and diagnosed choriocarcinoma is striking. It is due chiefly to the much higher curability rate of choriocarcinoma preceded by hydatidiform mole. Starting with a definition of choriocarcinoma as a neoplasm which if untreated kills, one arrives at three possible explanations for this higher curability rate of choriocarcinoma preceded by hydatidiform mole: 1. It is more easily cured because earlier diagnosed. 2. It is intrinsically less malignant, treated or untreated. 3. It is overdiagnosed as cancer, owing to the history of hydatidiform mole.

We ourselves would say that a preceding history of hydatidiform mole, while stimulating useful suspicion, unduly overweights the diagnosis in favor of cancer.

### INFLUENCE OF PARITY

The statement has frequently been made that the incidence of choriocarcinoma increases with the parity. Since, as we have shown, choriocarcinoma increases in frequency with age, and since, necessarily, parity also increases with age, this is true. It is necessary, therefore, to estimate the partial correlations of the incidence of choriocarcinoma with each factor; i. e., in this context, does choriocarcinoma occur with higher parity at any given age?

The difficulty of estimating this is in the fact that our figures are taken from the literature of several countries over several decades in which the average size of families has varied. As far as this country goes it is only since 1938 that the Registrar General's tables have given the number of preceding births for each instance of maternity. It is well known that the average size of families has been diminishing in the countries covered by our series, and, although it does not necessarily follow from this, it is reasonable to assume that over the years the parity for a maternity at a given age has diminished.

The Registrar General [6] published a table showing the number of cases of legitimate maternity in England and Wales in 1939, distinguishing age and total number of previous children of all marriages, i. e., showing the number of births of each parity at each age. We compared these figures with the corresponding frequencies from our series, reckoning only previous births, not pregnancies, for fatal and for diagnosed choriocarcinoma.

From this comparison it was found that for each age group women with choriocarcinoma did have a slightly higher parity than those in the normal 1939 population. Whether this slight increase compensates more or less for the increase in parity at each age which would be expected at the earlier decades partly covered in this series is a matter of judgment. We ourselves would infer from the figures here that the incidence of choriocarcinoma is not related to the parity of the mother. In any case the influence of parity cannot be great as compared with that of age.

### DEFINITION AND CURABILITY OF CHORIOCARCINOMA

Ewing [6b] stated, "I have been unable to find any record of operative cure of choriocarcinoma." Mathieu [7] has given a cure rate of 95 per

6. Ewing, J.: (*a*) Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940; (*b*) ibid., p. 637.

7. Mathieu, A.: Internat. Abstr. Surg. **68**:52 and 181, 1939.

cent for choriocarcinoma. It is true that Ewing's "choriocarcinoma" was one of his subdivisions of "chorioma," the one in which the growth was most cancerous, the others being simple hydatidiform mole, chorioadenoma destruens, syncytial endometritis and syncytioma. Nevertheless, it seems clear that these authors were describing different syndromes.

"Choriocarcinoma" is a poorly defined term. Ideally a complete definition would include a description of the course of the disease and the postmortem observations. As a clinical problem, however, choriocarcinoma may be understood in four possible ways, as may any other type of tumor:

1. *It is a tumor to be regarded as a cancer because it always kills.*

Thus defined, choriocarcinoma would be diagnosed only if past experience had shown that a syndrome could be found which, if untreated, always ended in death.

2. *It is a tumor to be regarded as a cancer because it shows the criteria of cancerous growth: infiltration and metastasis.*

For every other tumor in the body which does not show regression this and the preceding definition would be synonymous.

3. *It is a tumor to be regarded as a cancer because sometimes it infiltrates and metastasizes, and sometimes it kills.*

Sometimes there is reason to believe that choriocarcinoma, though producing a syndrome which is apparently identical with that of cancer otherwise, does not infiltrate or metastasize and resolves spontaneously.

4. *It is a condition the future behavior of which is irrelevant to the definition and the diagnosis, like, say tuberculosis.*

It is obvious that the first way of defining the tumor would be for pragmatic reasons the best. And indeed when choriocarcinoma or its treatment is discussed in a general sense the assumption is made that the tumor has in fact been defined in the first way. In the present state of knowledge most individual cases can be diagnosed only under definition 3. With most neoplasms, at any stage histologic and clinical data together can give a reliable estimate of the probability of cancer, i. e., a prognosis, so that definition-groups 1 and 3 coincide. With choriocarcinoma, however, this is not so, and unless this distinction is recognized the comparison of curability rates will be invalid.

Everyone is agreed that the diagnosis of choriocarcinoma is difficult, and indeed Hörmann[8] and Veit[9] held with some reason that choriocarcinoma can be diagnosed only after it has run its course to death. Choriocarcinoma is so rare that no one man can have a large series of cases all diagnosed with fixed standards. In the literature the standards by which the diagnosis "choriocarcinoma" is made vary enormously.

8. Hörmann, K.: Monatsschr. f. Geburtsh. u. Gynäk. **29**:198, 1909.
9. Veit, J.: Ztschr. f. Geburtsh. u. Gynäk. **44**:466, 1901.

Line 3 of table 1 gives the curability rates for choriocarcinoma following different types of pregnancy. Table 4 shows the curability rates with the same definition as in table 1 but classified by the decade in which the case report was published.

Table 4 shows clearly how the curability rate for choriocarcinoma has risen steadily since 1890 and how this rise may be attributed almost entirely to the group of cases in which choriocarcinoma is associated with hydatidiform mole. The following remarks may be made: 1. The form of treatment of choriocarcinoma has remained basically

TABLE 4.—*Changes in the Curability Rate of Choriocarcinoma During the Last Fifty Years*

| | Type of Pregnancy (See key below) | Decade | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | -1889 | 1891-1900 | 1901-1910 | 1911-1920 | 1921-1930 | 1931-1940 | 1941- | |
| Cases in which death was directly attributable to choriocarcinoma | 1 | 3 | 23 | 10 | 7 | 6 | 7 | 2 | 58 |
| | 2 | 3 | 17 | 23 | 2 | 5 | 5 | 1 | 56 |
| | 3 | 6 | 20 | 14 | 5 | 6 | 4 | 1 | 56 |
| | 4 | 0 | 2 | 1 | 1 | 1 | 6 | 1 | 12 |
| | 5 | 0 | 0 | 2 | 2 | 0 | 4 | 0 | 8 |
| | Total | 12 | 62 | 52 | 17 | 18 | 26 | 5 | 190 |
| Cases in which patient survived for six months and apparently was cured | 1 | .. | 6 | 8 | 3 | 0 | 2 | 1 | 20 |
| | 2 | .. | 10 | 14 | 7 | 8 | 10 | 2 | 51 |
| | 3 | .. | 25 | 19 | 10 | 22 | 34 | 16 | 126 |
| | 4 | .. | 2 | 0 | 1 | 1 | 2 | 0 | 6 |
| | 5 | .. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | .. | 43 | 41 | 21 | 31 | 48 | 19 | 203 |
| Curability rate per cent | 3 | .. | 56 | 58 | 67 | 79 | 89 | 94 | 69 |
| | All others | .. | 20 | 57 | 48 | 43 | 39 | 43 | 36 |
| | Total | .. | 41 | 44 | 57 | 63 | 65 | 79 | 51 |
| Total number of cases diagnosed (and reported) | 1 | 3 | 32 | 19 | 10 | 8 | 10 | 3 | 85 |
| | 2 | 3 | 29 | 46 | 14 | 17 | 20 | 4 | 133 |
| | 3 | 7 | 49 | 38 | 20 | 36 | 41 | 19 | 210 |
| | 4 | 0 | 5 | 1 | 2 | 2 | 9 | 1 | 21 |
| | 5 | 0 | 0 | 2 | 2 | 0 | 4 | 0 | 8 |
| | Total | 13 | 115 | 106 | 51 | 64 | 84 | 27 | 460 |

1 = Normal full term pregnancy. 2 = Hydatidiform mole. 5 = Type not known.
3 = Abortion. 4 = Tubal pregnancy.

unchanged. We have excluded from the table intraoperative and postoperative deaths, and all deaths which may not be directly attributed to choriocarcinoma as such, so that improvements in operative technic are not relevant. The improvement in the curability rate may be attributed only to earlier diagnosis or overdiagnosis. 2. Awareness and management of the possible sequelae of hydatidiform mole have increased and improved with general medical progress. Biologic tests for pregnancy have played a great part in this, but it has not always been realized that these tests assess only the presence of trophoblastic tissue, not the presence of choriocarcinoma. 3. Our figures are derived from reports in the literature. Reported cases tend to be definite, with a confirmed diagnosis, and are described by authors specially interested or specially

competent. Probably these figures greatly underestimate the proportion of diagnosed and nonfatal cases. The apparent curability rate is probably even higher than the 79 per cent shown for 1941 onward in table 4. It is difficult to believe that a neoplasm with so grave a prognosis as choriocarcinoma can have such a strikingly higher cure rate than other active carcinomas treated by operation.

There is no proof that choriocarcinoma following hydatidiform mole is more active than choriocarcinoma following other types of pregnancy, and yet there is no doubt that with an equally suspicious clinicopathologic picture a history of preceding hydatidiform mole causes undue bias toward a diagnosis of cancer.

We ourselves would infer from these figures that the better curability rate is to a great extent the result of erroneous overdiagnosis of choriocarcinoma following hydatidiform mole.

### DURATION OF GESTATIONAL CHORIOCARCINOMA

In our later notes of the reports in the literature a record was made of the time between cessation of pregnancy and diagnosis and the time between diagnosis and death if this occurred. Since the figures cover only the later papers read, they are incomplete but still a fair sample. Often the time of an abortion could be determined only with difficulty and it was estimated approximately.

For the time of diagnosis we chose, whichever came first, (*a*) the time of hysterectomy, or (*b*) the time when it was decided that the tumor was inoperable, usually because metastases were present, or (*c*) the time of autopsy in those cases in which tumor was diagnosed at or immediately before death. All cases in which the latent period between the end of pregnancy and the diagnosis was more than three years have been excluded. These cases are treated separately in table 5. The following results were obtained.

A. Straightforward cases in which the patient was treated by hysterectomy, with recovery: 82.
   Mean time between cessation of pregnancy and hysterectomy: 4.7 months.
   (If 6 cases in which hysterectomy was not carried out until more than 12 months after cessation of pregnancy are eliminated the mean time is 3.6 months.)

B. Straightforward cases in which the patient was treated by hysterectomy, with postoperative death: 22.

C. Straightforward cases in which the patient was treated by hysterectomy, with death from generalized metastases: 31.
   Mean time between cessation of pregnancy and hysterectomy: 7.6 months.
   (If 5 cases with a time interval of more than 12 months are eliminated, the mean time is 4.7 months.)
   Mean time between hysterectomy and death: 4.4 months.

(In 5 cases the time was less than 1 month; in 1 each, it was 9, 10 and 11 months, and in 2, 12 months.)

D. Cases inoperable or with metastases at time of diagnosis: 23.

Mean time between cessation of pregnancy and diagnosis: 5.0 months. (If 2 cases with a time interval of more than 12 months are eliminated, the mean time is 3.6 months.)

Mean time between date of diagnosis and death with generalized metastases: 2.3 months.

3 cases in which the patient presented a vaginal nodule and recovered after treatment are not included.

E. Cases diagnosed at autopsy or just before death: 60.

Mean time between cessation of pregnancy and death: 6.1 months. (If 4 cases with a time interval of more than 12 months are eliminated, the mean time is 5.4 months.)

From these figures it can be seen that choriocarcinoma, once it has been diagnosed, kills in an average time of about four months. In no case was there an interval of more than twelve months between diagnosis and death. It appears significant that in those straightforward cases with hysterectomy, diagnosed at a mean time of 4.7 months after cessation of pregnancy, the patient recovered and that in those diagnosed at a mean time of 7.6 months the patient died. Before accepting this as evidence that earlier diagnosis gives a higher curability rate one must note that for those cases in which there was an inoperable growth or metastasis at the time of diagnosis, the mean interval between cessation of pregnancy and diagnosis was only 5.0 months; and that for those cases diagnosed at death, this interval was only 6.1 months. Moreover, it is probable that there is a correlation between earliness of diagnosis and overdiagnosis, so that it cannot be known that the cases in which hysterectomy was followed by recovery were clinically similar before operation to the cases in which death occurred subsequent to hysterectomy; or, if they were not, that this itself might not account for the difference between 4.7 and 7.6 months.

If an inference can be made, it would be that choriocarcinoma is an acute disease, rapidly fatal but with a variability which in many of the cases with a more prolonged interval allows time for diagnosis and treatment before it reaches the stage of inoperability or recognizable metastasis. We would not be prepared to draw the conclusion that hysterectomy is of value in curing or postponing death.

## DEFINITION

To the abnormal trophoblastic proliferations occurring during and after pregnancy, Ewing [10] gave the generic title "chorioma." Chorioma, like any type of tumor, shows a gradation in respect to (*a*) rate of cellular proliferation, (*b*) extent of spread and (*c*) "malignant" charac-

10. Ewing, J.: Surg., Gynec. & Obst. **10**:366, 1910.

ters, i. e., infiltration and metastasis so far as these can be separated from rate of cellular proliferation. By this definition the hydatidiform mole, inasmuch as it shows trophoblastic proliferation, is a chorioma. To a chorioma that kills by extent of infiltration and metastasis may be given the specific term "choriocarcinoma." It does not follow from this definition that a choriocarcinoma is necessarily diagnosable before the death of the patient.

## RELATIONSHIP OF HYDATIDIFORM MOLE AND CHORIOCARCINOMA

Hydatidiform mole is generally accepted as a precancerous lesion. For purposes of discussion it can be taken that the classic hydatidiform mole occurs once in every 2,000 pregnancies, and that choriocarcinoma preceded by hydatidiform mole is one to two times as frequent as choriocarcinoma preceded by normal pregnancy. It follows from this that for a pregnant woman the risk of sequent choriocarcinoma is 2,000 to 4,000 times greater after hydatidiform mole than after normal pregnancy. There are also, however, the significant facts that in 50 to 60 per cent of cases choriocarcinoma is not preceded by hydatidiform mole, and that in 90 to 99 per cent of cases hydatidiform mole is not followed by choriocarcinoma—percentages which indicate clearly that the association is not complete.

The role conventionally assigned to hydatidiform mole in the genesis of choriocarcinoma is that of a precancerous lesion somewhat analogous to leukoplakia vulvae or villous papilloma of the bladder. The analogy, however, is not appropriate.

A leukoplakia which is going to become cancerous shows a gradual sequence of changes in time which can be observed and predicted. If many patients with leukoplakia-carcinoma are examined, all gradations both in rate of change and in extent of change can be seen. The link in the chain and the essential feature in both leukoplakia and carcinoma is the epithelial hyperplasia. On the other hand, no one can yet say for certain which of a series of hydatidiform moles will become cancerous and which not. There is no gradation of changes by which a causal sequence might be inferred, either in individual cases or in the class as a whole.

In fact, the real analogy is not between hydatidiform mole and such a process as leukoplakia vulvae but between hydatidiform mole and, say, an apparently idiopathic pleural effusion in an elderly person. Just like hydatidiform mole, this effusion is mostly a sign of a noncancerous process; but in some cases, just as in some cases of hydatidiform mole, a frank cancer later manifests itself. The parallel may be completed by adding that primary or secondary cancer of the lung frequently does not cause pleural effusion and that the size of an effusion is

no indication of the likelihood of cancer. This analogy may seem glib, but it really does not strain the logical implications of the known facts of the hydatidiform mole–choriocarcinoma relationship.

Every hydatidiform mole necessarily shows hydrops, but it is also true that nearly every hydatidiform mole also shows trophoblastic hyperplasia. No one has yet given any plausible reason for the coexistence of these two features. Pathologically, the second is not less important than the first. Most of the discussion on the nature of hydatidiform mole has centered around the cause of the hydrops, probably because hydropic changes are at least susceptible of explanation in terms of mechanical and nutritive factors. Epithelial hyperplasia is as unexplainable as cancer itself and has thus come to be regarded as of secondary importance. The statement has been made that the epithelium undergoes hyperplasia as a secondary response to the distention of the villus. The only evidence for the hyperplasia being sequent to the hydrops is its coexistence, and usually one would regard epithelial hyperplasia in association with local edema as causally antecedent.

One unifying concept of the hydatidiform mole–choriocarcinoma relationship would be that hydatidiform mole had many causes in which a dysfunction, possibly malnutritive, at the fetal-maternal junction was the common factor. Of these causes, an already existent choriocarcinoma would be one, or else a not yet existent choriocarcinoma but its carcinogenic precursors. Otherwise it is necessary to accept two completely independent chains of causation, each starting with fertilization of the ovum and ending with choriocarcinoma. In one the sequence is fertilized ovum → villous tissue with hydrops → trophoblastic hyperplasia → choriocarcinoma. In the other the sequence is fertilized ovum → villous tissue without hydrops but with trophoblastic hyperplasia → choriocarcinoma.

It may be that these two chains of causation, which differ only in the presence of hydropic villous change, have in fact completely independent mechanisms. Two features, however, appear in each—trophoblastic hyperplasia and a precancerous state. This may be accidental, but the temptation is strong to regard the development of the hydropic elements of a hydatidiform mole as a more or less irrelevant by-product or sideline in the process which starts with conception and ends in choriocarcinoma.

## HORMONAL FACTORS

### BIOLOGIC TESTS FOR PREGNANCY

The true positive reaction of Aschheim and Zondek [11] consists in the concurrent appearance of three changes in the ovaries of the test animal:

(a) Ripening of follicles (APR [11a] 1),

11. Aschheim, S., and Zondek, B.: Klin. Wchnschr. **7**:1404 and 1453, 1928.
11a. APR means anterior pituitary reaction.

(*b*) Hemorrhage producing "blood spots" *(Blutpunkte)* about the size of a pinhead in some unruptured follicles (APR 2).

(*c*) Luteinization of follicles in which the ova are retained—atretic corpora lutea (APR 3).

In practice the test is considered positive for pregnancy if there is any evidence of either APR 2 or APR 3 in any of the test animals, i. e., a single hemorrhagic follicle or a corpus luteum (Selye [12b]). Hemorrhagic follicles are also the sign of a positive Friedman test.

*Specificity of Biologic Pregnancy Tests in General.*—APR 1 by itself is not specific for pregnancy. It can be obtained (*a*) after castration of a person of either sex, (*b*) during and after the menopause, (*c*) with elderly men and (*d*) with some men showing testicular tumors (Twombly, Temple and Dean [13]; Brewer [14a]; Selye [12a]) and is due to increased excretion of the follicle-stimulating hormone of the pituitary gland—the so-called "castrate" response.

APR 2 and APR 3 are given by "chorionic gonadotropin." There appears to be a majority of opinions agreeing that during pregnancy "chorionic gonadotropin" is produced in the placenta and not in the pituitary gland, though Newton [15b] pointed out that the problem is strictly unanswerable since "hypophysectomy is unlikely to be performed on a pregnant woman and would in any case almost certainly terminate the pregnancy." There is, moreover, a difference of opinion concerning the nature of the hormone. The point at issue is whether the placental hormone is or is not identical with the luteinizing hormone produced normally by the pituitary gland at times other than during pregnancy.

Best and Taylor [16a] stated that pregnancy urine produces in assay animals reactions differing from those produced by anterior pituitary transplants and extracts. They remarked,[16b] "Collip and his associates have shown the latter [i. e., the active principle in pregnancy urine] to be identical with the gonadotropic substance of the placenta, and have named it the *anterior-pituitary-like substance*. It is now more commonly spoken of as *chorionic gonadotropin.*" On the other hand, Selye regarded chorionic gonadotropin as identical with the pituitary luteinizing hormone since in his classification of pituitary hormones he had the heading "LUTEINIZING HORMONE. *Synonyms:* interstitial-cell-stimulating hormone, chorionic gonadotropin, metakentrin." [12c] He also stated

12. Selye, H.: (*a*) Textbook of Endocrinology, Montreal, Canada, Univ. Montreal, 1947; (*b*) ibid., p. 221; (*c*) p. 209; (*d*) p. 254; (*e*) p. 819.

13. Twombly, G. H.; Temple, H. M., and Dean, A. L.: J. A. M. A. **118**:106, 1942.

14. Brewer, J. I.: (*a*) Arch. Path. **41**:580, 1946; (*b*) ibid., p. 589.

15. Newton, W. H.: (*a*) Physiol. Rev. **18**:419, 1938; (*b*) ibid., p. 427.

16. Best, C. H., and Taylor, N. B.: (*a*) The Physiological Basis of Medical Practice, ed. 4, London, Ballière, Tindall & Cox, 1945; (*b*) ibid., p. 758.

later [15a] that the placenta contains and secretes luteinizing hormone as well as other hormonal substances. The matter is clearly controversial. The significance of the debate is this: If the pituitary luteinizing hormone and chorionic gonadotropin are identical, the range of disorders in which a fully positive biologic pregnancy test response may be obtained is greatly widened, and the specificity of this response correspondingly reduced.

Abnormal excretion of luteinizing hormone may occur in many conditions other than the pregnancy states and the so-called choriocarcinoma of ovary and testis. Of these, Selye [15a] mentioned dysgerminoma of the ovary and seminoma of the testis as well as testicular and ovarian teratoma, also the state of pseudopregnancy with corpus luteum cysts. While these states are probably unlikely to cause confusion often, Newton [15a] cited others as having obtained the fully positive Aschheim-Zondek reaction with the urine of women in whom chorionic tissue was not present (Phillip [17]) or who had passed the menopause (Neumann [18]).

Selye [15a] gave a further list of conditions occasionally associated with increased excretion of gonadotropin though not specifying whether the follicle-stimulating or the luteinizing hormone predominates. Among them are male hypogonadism, anterior pituitary tumors, increased intracranial pressure, anatomic lesions of the hypothalamus, and adrenocortical tumors.

There are other conditions, about which we have been unable to find information, which, one would think, might quite likely be accompanied sometimes by a fully positive Aschheim-Zondek reaction. These include secondary tumors of brain and adrenal gland and primary or secondary tumors of the kidney that mechanically interfere with adrenal function.

In the views put down so far in this section we have assumed that APR 1 (due to the follicle-stimulating hormone) is always distinguished accurately from APR 2 and APR 3 (due to luteinizing hormone). Doubt has been voiced, particularly by workers on testicular tumors (e. g., Twombly, Temple and Dean,[15] Francis [19] and Brewer [14a]), whether this distinction is invariably made. Francis, for example, made the comment that there is much variation in the technic of the Aschheim-Zondek test and that, amongst other things, interpretation of the ovarian changes is empiric and variable. If this is valid for testicular tumors, it is valid for any other hormonal dyscrasia, and if the grounds for doubt are sound, one must be prepared to accept the follicle-stimulating

17. Phillip, E.: Zentralbl. f. Gynäk. **54**:3076, 1930; cited by Newton.[15a]

18. Neumann, H. O.: Klin. Wchnschr. **13**:1278, 1934; cited by Newton.[15a]

19. Francis, R. S.: Brit. J. Surg. **33**:173, 1945

hormone as a possible producer of a positive Aschheim-Zondek reaction. The ways in which this would further reduce the specificity of the reaction are obvious.

The significance of a positive reaction in any given biologic test for pregnancy depends, of course, on accompanying circumstances to a greater or less degree. In the great majority of cases interpretation is straightforward. When a sample of urine from a healthy woman regarded as probably pregnant is reported as yielding a positive reaction, it is unlikely that the reaction indicates anything but pregnancy. But this high degree of probability for pregnancy would be completely altered if, for example, a specimen of urine were submitted from a woman in whom there was some reason to suspect an ovarian tumor. The probability that a positive reaction in these circumstances stands for pregnancy would be low, and the probability that it indicates a gonadal tumor of the ovary high.

In other words, all that an Aschheim-Zondek reaction affirms is that one of the conditions which produce a reaction in the Aschheim-Zondek test is present. The decision whether this condition is specifically pregnancy or choriocarcinoma or any other state depends on the clinical findings.

*Specificity of Biologic Pregnancy Tests in Different States of Pregnancy.*—There is general agreement on the reliability of biologic pregnancy tests in diagnosing an existent pregnant state—on accuracy of 98 to 99 per cent. The particular interest here is in their ability or inability to distinguish between normal or tubal pregnancy, hydatidiform mole and choriocarcinoma, and retained tissue or metastases from any of these states.

Since chorionic tissue is common to all these conditions, one might expect any differences to be quantitative only, not qualitative. Attempts have in fact been made to discover and evaluate qualitative differences. Smith and Smith,[20] for example, found a comparatively low estrogen content in blood and urine from patients with choriocarcinoma and hydatidiform mole and suggested that ". . . the chorionic cells themselves, when they become neoplastic, do not contain oestrin in amounts comparable with those in the normal placenta." It appears, however, that work along these lines has not developed a practical value, for eight years later Hamburger [21a] expressed the opinion that it is unlikely that analysis of the excretion of estrogenic and androgenic substances, or any other improvements in technic, will be of much help in the diagnosis of hydatidiform mole.

20. Smith, G. van S., and Smith, O. W.: Proc. Soc. Exper. Biol. & Med. **22**:847, 1935, p. 849.

21. Hamburger, C.: (*a*) Acta. obst. et gynec. Scandinav. **24**:45, 1943; (*b*) ibid., p. 79.

With regard to the value of quantitative estimations, choriocarcinoma and hydatidiform mole would tend in a broad series of cases to show higher levels of chorionic gonadotropin in blood and urine than in normal pregnancy or with simple placental remnants; but this is of little value in a single instance. Mathieu [22] has said, "There appears to be a misconception that an increase of the ordinary amount of prolan in the urine of the pregnant woman indicates decisively that hydatidiform mole or chorioepithelioma is present. This is a fallacy and should not be perpetuated."

It is clear that the time factor must play a big part in assessing the significance of any hormonal assays in pregnancy. Boycott and Smiles [23] and earlier workers have pointed out that in normal pregnancy there is an exceedingly high hormone peak lasting for two to three weeks at about the sixtieth day of pregnancy, which is about the time in pregnancy when hydatidiform mole is likely to be expected. This period of high gonadotropin excretion does seem to have been a source of confusion in the past before it was recognized as normal.

Even allowing for this hormone peak one encounters anomalies. Fluhmann,[24] for instance, has mentioned cases in which hydatidiform mole was associated with little or no excretion of gonadotropin and other cases in which a metastasizing choriocarcinoma was accompanied by excretion of smaller amounts of gonadotropin than accompany a normal pregnancy.

Variations in technic can hardly explain these anomalies or provide a reason why quantitative readings are of so little help. The reason must be either that the hormone-producing tissue varies in activity or that the inactivating and/or excretory mechanisms vary in efficiency from patient to patient.

Hamburger's [21a] recently expressed opinions on the practical application and interpretation of biologic tests for pregnancy may, we should think, be taken as current and authoritative. He said that it is not practicable for a diagnosis of hydatidiform mole to be made with certainty by hormonal analysis, and he set out what he expressed as "the most expedient regimen" for the hormonal control of the patient with hydatidiform mole. He stated that after removal of a hydatidiform mole a rising level of urinary gonadotropin or a titer greater than 30,000 international units per liter at least one month after the removal, or excretion of gonadotropin persisting more than three to five months, are individually suggestive of "complications"—not, it may be noted, of any specific state. These complications include cancerous choriocarcinoma and simple molar remnants; and one of his final conclusions [21b] is that

22. Mathieu, A.: Surg., Gynec. & Obst. **64**:1021, 1937, p. 1022.
23. Boycott, M., and Smiles, J. M.: Lancet **1**:1428, 1939.
24. Fluhmann, C. F.: Am. J. Obst. & Gynec. **33**:931, 1937.

". . . it appears not to be practicable by hormonal analyses to decide the nature of the complications."

It is clear that a "positive Aschheim-Zondek reaction" cannot be accepted as conclusive proof in almost any context of the presence of choriocarcinomatous tissue. A reaction in a given hormonal test for pregnancy has only a probability value, greater or less depending on circumstances. Once this probability has been assessed and added to the other probabilities in the case, the result of such a test is without question of great value.

*Biologic Pregnancy Tests in Relation to Testicular Tumors.*—Biologic pregnancy tests were first used in investigating disease in the male by Zondek,[25] in 1930. Heidrich, Fels and Mathias [26] also used the technic in the same year in investigating a case of testicular tumor. Yet, as Burrows [27] commented, attempts to distinguish choriocarcinoma from other kinds of testicular tumor by means of the Aschheim-Zondek test have not been so successful as had been hoped.

The subject has been discussed in detail by Twombly,[28] Francis [15] and Brewer.[14a] It appears that there is only an approximate correlation between the type of testicular tumor being examined and the test animal's ovarian response to injection of the urine. There is difficulty in the fact that three types of response may be found, "pure luteinizing," "pure follicle-stimulating" and "mixed"; that responses may vary in test animals of different species, and that a distinction has not always been made in different laboratories between the various types of response.

Over a broad selection of cases the "chorionic" type of hormone is more particularly associated with the choriocarcinomatous type of growth, while the follicle-stimulating or "castrate" type of hormone is apt to be associated with seminoma. It is evident that the presence in a testicular tumor of tissue morphologically resembling true pregnancy choriocarcinoma does not imply necessarily the coexistence of a "true" pregnancy response in a biologic test, and vice versa.

## SOURCE OF CHORIONIC GONADOTROPIN

The current view on this matter has been summarized by Brewer [14b]:

All the evidence, both clinical and experimental, indicates that the chorionic gonadotropin is produced by chorionic tissues, that the tissues of the embryo proper do not produce the hormone, that no other tissues are known to produce it, that when the hormone is present in instances of testicular tumor it is identical with the

25. Zondek, B.: Klin. Wchnschr. **9**:679, 1930.

26. Heidrich, L.; Fels, E., and Mathias, E.: Beitr. z. Klin. Chir. **150**:349, 1930; cited by Burrows.[27]

27. Burrows, H.: Biological Actions of Sex Hormones, London, Cambridge University Press, 1945.

28. Twombly, G. H.: Surgery **16**:181, 1944.

chorionic gonadotropin found in the urine in pregnancy and that in these instances it is produced by the tumor tissues.

As already mentioned, most theories support a placental origin for chorionic gonadotropin. Many kinds of tissue combine to make up the placenta, and it would be well to see if there is evidence to show which of the various tissues produces the hormone. There are at least three lines of approach: tissue culture experiments, cytologic studies of the placenta and observations in lower animals.

*Evidence from Cultures of Placental Tissues.*—Tissue culture experiments have been carried out by Gey, Seegar and Hellman [29] and by Jones, Gey and Gey [30] on tissues from normal placentas of varying age and from hydatidiform moles. Both groups of workers concluded that the Langhans cells were the probable source of chorionic gonadotropin. Tissue from hydatidiform moles showed no significant difference in hormonal activity from normal placental tissue.

*Evidence from Cytologic Studies of Placenta.*—Wislocki and Bennett [31a] and by Dempsey and Wislocki [32] made detailed cytologic studies of placenta but came to no definite decision regarding the source of chorionic gonadotropin. Reviewing the evidence given by cytologic studies and experimental cultures Wislocki and Bennett said [31b]:

> Considering all aspects of the possible clues presented . . . we are willing to suggest in a speculative and purely tentative manner that the chorionic gonadotrophic hormone derives from the cytotrophoblast rather than from the syncytium.

*Observations in Lower Animals.*—Catchpole and Lyons [33] and Cole and Goss [34] made detailed investigations into the source of equine gonadotropin. Catchpole and Lyons concluded that the gonadotropin was produced by chorionic tissue but that the most potent source of the hormone was fertile endometrium. Endometrium in contact with chorion was much richer in gonadotropin than endometrium in the infertile horn, although there was progestational proliferation in both. Cole and Goss discussed these findings and concluded from their own experiments that equine gonadotropin is produced by maternal tissue and can be demonstrated in highest concentration in the secretion of specialized endometrial structures, that it is present also in lesser amount in the

29. Gey, G. O.; Seegar, G. E., and Hellman, L. M.: Science **88**:306, 1938.

30. Jones, G. E. S.; Gey, G. O., and Gey, M. K.: Bull. Johns Hopkins Hosp. **72**:26, 1943.

31. Wislocki, G. B., and Bennett, H. S.: (*a*) Am. J. Anat. **73**:335, 1943; (*b*) ibid., p. 411.

32. Dempsey, E. W., and Wislocki, G. B.: Endocrinology **35**:409, 1944; Am. J. Anat. **76**:277, 1945.

33. Catchpole, H. R., and Lyons, W. R.: Am. J. Anat. **55**:167, 1934.

34. Cole, H. H., and Goss, H.: In Essays in Biology, Berkeley, Calif., Univ. California Press, 1943, p. 105.

endometrium between these structures and that there is strong evidence against its being produced by chorionic tissues.

This is the only evidence we have been able to find which separates with some accuracy fetal and maternal factors in the production of a placental gonadotropin. It suggests that in the mare at least maternal tissue is the source of origin.

## HISTOLOGIC ASPECT OF CHORIOCARCINOMA

The possible histologic factors diagnostic of choriocarcinoma—excess or deficiency of syncytium or of Langhans' cells, stromal changes in the villi, hemorrhage, necrosis, invasion of blood vessels, endometritis, giant cells and the like—have been discussed for many years. None has been found reliable. This indicates the positive and now accepted fact that morphologically trophoblast with a benign future is exactly like trophoblast with a cancerous future. It has also been made clear that, apart from their forming the distinctive pattern of trophoblast, there is no way of distinguishing embryonic cells from maternal cells within the maternal tissue.

The tissues concerned at the placental site can be discussed as follows.

### DECIDUA

Although decidua is endometrial stroma in its transformed pregnancy state, it can look strikingly epithelioid. It can, in fact, resemble squamous epithelium. Formerly the main argument against choriocarcinoma being "deciduoma malignum" was its carcinomatous appearance. Histologists have now much more generous ideas of the capacity of tissues for metaplasia and interchangeability of morphologic characters, and that argument, reconsidered in the climate of present day opinion, is not nearly so strong.

### TROPHOBLAST

Trophoblast is quite distinctive, and so is decidua, yet if these two different and distinctive tissues are in contiguity, no sharp line can be drawn between them so that one can say this cell or that cell is maternal or fetal. In describing early placentation in the macaque, Wislocki and Streeter,[35b] in referring to the appearances at the placental interface, commented:

> Difficulty arises, at this period, in assigning exact limits to the boundaries of the bases of the cell columns, and one becomes confused in traversing the junctional zone from its fetal to endometrial boundaries as to which exactly of the cellular elements are fetal and which maternal. There is no sharply differentiating stain so far developed to distinguish the two, and on morphology of nucleus and cytoplasm they cannot be separated with precision.

35. Wislocki, G. B., and Streeter, G. L.: (*a*) Contrib. Embryol. **27**:1, 1938; (*b*) ibid., p. 23.

Von Fellner (quoted by Hörmann [*]) held that decidual cells could not be distinguished from Langhans' cells and "proved" their identity by tracing one into the other by serial sections.

In the normal placenta there is, of course, the fibrinoid layer of stria, of Nitabuch. Mostly this separates frank trophoblast from frank decidua, but even here, and certainly in such sections of normal placental sites as we have examined, cells may lie in its wider zones which cannot be allocated with certainty to one side or the other: and the same can be said of the junctional zone in many examples of the trophoblastic hyperplasias.

This similarity of tissue might be quite coincidental. A sheet of large epithelial cells is not very different from a sheet of large decidual cells looking like epithelial cells, especially when there is more or less polymorphic degeneration in each. Another explanation of the gradation would be that the pregnancy process which converts the endometrial constituents into a mass of indistinguishable large cells acts equally on the genetically different fetal tissue to produce a similar morphologic change. Another way of putting this would be to say that pregnancy endometrium expresses its different functions in different modes and that some of what we call trophoblast represents the mode in which the endometrium functions adjacent to the embryo. This would mean that maternal cells intermingled with, and subject to the same local influences as, fetal cells, and perhaps carrying out the same functions, would assume the same morphologic appearances. There can be little doubt that physiologic trophoblast is fetal in origin. On the other hand, there is much in the behavior of the chorionic neoplasm which can best be explained on the basis of a maternal origin for the component cells.

Marchand [36] himself said that ". . . the concept that the elements of cytotrophoblast arise from decidual cells has at first sight so much to be said for itself that I myself was for some time of this opinion. . . ." He changed his opinion because of the avascularity of trophoblast, because of certain distinctions between the nuclei and because in his view decidual cells are never so epithelially arranged as in trophoblast. The significance of these distinctions is at least arguable, yet Marchand's work is the basis on which the fetal concept of choriocarcinoma was founded.

### GIANT CELLS AT THE PLACENTAL SITE

These cells have been defined by Mossman [37b]: ". . . by uterine giant-cells we refer to any unusually large cells occurring in the uterus or fetal membranes whether they be mononuclear or polynuclear and of maternal or fetal origin."

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36. Marchand, F.: Monatsschr. f. Geburtsh. u. Gynäk. **1**:419, 1895, p. 434.

37. Mossman, H. W.: (*a*) Contrib. Embryol. **26**:129, 1937; (*b*) ibid., p. 170.

The nature of placental giant cells forms a big and still debated subject. There are at least six possible sources—muscle, vascular endothelium, decidua, cytotrophoblast, syncytiotrophoblast, maternal epithelium—and there is no doubt that all of these can produce giant cells, especially in conditions conducing to tissue degeneration. In spite of many attempts over the years there is no way of deducing for certain the tissue of origin of an individual giant cell at the placental site. The fact that no one has shown a certain distinction between giant cells of fetal origin and giant cells of maternal origin—and there can be little doubt that many of them are in fact of maternal origin—emphasizes the morphologic similarity which these tissues assume when at the same site and presumably when subject to the same influences.

### TROPHOBLAST IN CHORIOCARCINOMA

The lesion characteristic of choriocarcinoma is a ragged, hemorrhagic nodule, 0.5 to 4 cm. or more in diameter—what may be called a trophoblastic node. Histologically this consists mainly of blood clot. In this, mostly at the periphery, there is usually more or less of a tissue which cannot be distinguished from the hyperplastic trophoblast surrounding a hydatidiform villus. There are some outliers of trophoblastic tissue in the surrounding myometrium, and a variable amount of necrosis and fibrinoid degeneration. If the nodule abuts on the endometrial surface or protrudes into the uterine cavity, there will be more or less inflammatory changes superadded. This histologic picture is remarkably constant no matter what the clinical outcome.

### MITOTIC FIGURES

Novak [38] mentioned the absence of mitotic figures as almost typical of choriocarcinoma, and indeed there is no doubt that in many cases cancerous choriocarcinoma does not show mitoses. It is remarkable that this, the fastest growing or at least the most quickly lethal of all cancers, has the smallest accompaniment of mitoses. The general question of the relation of the mitotic count to what seems to be actual increase in the number of cells is difficult and obscure. It certainly seems that some tissue proliferations have for a given cell increase a higher mitotic count than others. It may be that the excessive hemorrhage associated with trophoblast causes a bulkiness of the lesion and a lethality of effect quite disproportionate to the number of cells engaged. For an equal number of cells a trophoblastic node must be many times the size of a metastatic nodule of mammary carcinoma. This observation could explain the infrequency of mitoses and the coexistence of the infrequency of mitoses with rapid lethality.

38. Novak, E.: Gynecological and Obstetrical Pathology, ed. 2, Philadelphia, W. B. Saunders Company, 1947.

Most phases of the mitotic cycle can be imitated perfectly by nuclear pyknosis and karyorrhexis. For the assessment of mitoses occurring in tissue subject to degenerative changes it is essential, therefore, that some at least of the mitoses should be unequivocal diasters.

Using this rigid criterion, we took our 72 slides from cases of diagnosed or suspected choriocarcinoma, shuffled them, renumbered them so that we did not know which was which, and assessed the mitotic frequency of each, classifying the frequency as nil, occasional, moderate or excessive. The results are given here in outline. (The case numbers refer to those described in detail in table 4.)

*Nil:* All cases (including 3 in which the patients died with general metastases) except 8.

*Occasional:* A case that is not reported: Mitoses were in curettings of a hydatidiform mole. No hysterectomy. Patient alive and well.

Case 9. In the vaginal nodule and in the trophoblastic node. Patient died four and one-half months later with general metastases.

Case 18. In curettings and in the trophoblastic node from the excised uterus. Patient alive and well.

*Moderate:* Case 3. In the trophoblastic node from the excised uterus, and "occasional" in the previous curettings. Patient alive and well.

Case 8. In the trophoblastic node from the excised uterus. Patient died one month later with general metastases.

Case 15. In the trophoblastic node from the excised uterus. Patient died five years later, almost certainly from metastases of a mammary carcinoma.

Case 16. In the trophoblastic node from the excised uterus, and "occasional" in the previous curettings. Patient alive and well.

*Excessive:* Case 11. In the curettings, and "moderate" in the trophoblastic nodes from the excised uterus and vagina. Patient died five months later with general metastases.

From these data it appears that mitoses have some association with cancer, or perhaps rapidity of growth, but diagnostically this is of little help.

Only 5 curettings showed mitoses. Of the patients, 1 did not even have hysterectomy and is alive and well; 3 had trophoblastic nodes in the myometrium, and 1 of these patients, in the broad ligament as well. All are alive and well. In 1 patient the changes progressed to death with general metastases.

Only in 7 cases were mitoses observed in trophoblastic nodes in the tissues. Of the patients, 4 died with general metastases.

The tissues in case 11 were notable in this context. There was curetted tissue which showed polymorphism of the cells and a mitotic frequency which would have been striking in any cancer, and in this context was compatible only with cancer. The mitoses, although irregular, were not bizarre. Mitoses were still numerous in the excised uterine and vaginal nodules although not with the excessive frequency noted in the curettings.

### SYNCYTIUM

The main value of syncytium is the help it gives in the identification of trophoblast. It offers little help in the assay of changes that may be cancerous. We have an impression that in the trophoblast of nodes to be associated with cancerous devolution the proportion of syncytium relative to Langhans' cells is rather lower than usual. Schmauch [39a] said of syncytial giant cells that "the pycnotic condition of their nucleus speaks against any proliferative tendency," and he made two remarks on histologic appearances in general: "the more Langhans' cells the worse the prognosis." [39b] "In syncytial cases the prognosis is the better the more the syncytial masses and cells prevail." [39c]

### CORRELATION BETWEEN HISTOLOGIC OBSERVATIONS AND CANCER

Besides the original work of Marchand [40] the principal articles dealing with the detailed histology of choriocarcinoma are those of Teacher,[1] Schmauch,[40a] Ewing,[10] Geist,[41] Novak,[42] Meyer,[43] Williams [44] and Laqueur.[45]

Broadly speaking, all these authors have agreed in dividing abnormal trophoblastic proliferations into three classes: (*a*) benign overgrowth, usually in connection with hydatidiform mole; (*b*) locally destructive overgrowth, and (*c*) cancerous overgrowth of metastasizing potential. Laqueur's classification varies slightly in that it gives significance to differing behavior of trophoblastic tissue irrespective of the presence or the absence of hydrops of the villi. He divided the process into (*a*) chorionic invasion, (*b*) chorionic proliferation together with villous stroma and (*c*) chorionic proliferation without villous stroma.

*Presence of Chorionic Villi.*—There is general agreement that the presence of villi strongly suggests that an otherwise suspicious growth is noncancerous, though most authors add a caveat that it cannot be held to exclude choriocarcinoma with certainty.

As each reported case was studied, a note was made when there was specific mention of villi having been present in either the diagnostic curettings or the removed uterus. Complications were, first, the category of cancerous or invasive hydatidiform mole, and, second, insufficient histologic data in many cases. For these reasons the figures must be regarded as only very approximate.

39. Schmauch, G.: (*a*) Surg., Gynec. & Obst. **5**:259, 1907, p. 272; (*b*) p. 276; (*c*) p. 277.

40. Marchand, F.: (*a*) Monatsschr. f. Geburtsh. u. Gynäk. **1**:419 and 513, 1895; (*b*) Ztschr. f. Geburtsh. u. Gynäk. **32**:405, 1895; (*c*) **39**:173, 1898.

41. Geist, S. H.: Surg., Gynec. & Obst. **32**:427, 1921.

42. Novak, E.: J. A. M. A. **78**:1771, 1922.

43. Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. **92**:259, 1928.

44. Williams, T. J.: Am. J. Obst. & Gynec. **45**:432, 1943.

45. Laqueur, W. A.: J. Obst. & Gynaec. Brit. Emp. **52**:468, 1945.

Excluding the 47 examples of invasive hydatidiform mole (presented in detail on page 55), of which only 2 or perhaps 3 were followed by metastatic spread and death, we find that of 460 cases villi were specifically mentioned as present in 16:

12 with preceding history of simple hydatidiform mole: 11 nonfatal; 1 fatal with generalized metastases from choriocarcinoma.

4 with no history of hydatidiform mole: 2 nonfatal; 2 fatal (1 from unknown cause; 1 postoperatively but with general metastases at autopsy).

Among our own 23 cases villi were present in the removed uterus in 8. Of the patients, none died, although 2 at least had frank intramuscular trophoblastic nodes.

There can be no doubt that per se the presence of chorionic villi is a strong prognostic indication that the finding is not cancer.

*Invasion of Maternal Tissue.*—Meyer [46] was one of the earlier workers to emphasize that giant cells of "chorionic" type may be found deep in the decidua or the myometrium as part of the process of normal placentation, most numerous at the fourth to the fifth month and then decreasing. He also observed that so long as villi are present in a uterus containing retained products of pregnancy the discovery of epithelium deep in the muscle or even breaking through the walls of blood vessels may signify a harmless process and should suggest simple retention rather than a cancer. The opinions of Teacher, Schmauch, Novak, Laqueur and others are similar.

Ewing's category of syncytial endometritis, and to a lesser extent that of syncytioma, consists in the main of excessive giant cell formation, but it is not easy to decide to what extent this may be an effect of the described accompanying inflammatory reaction and not a condition in its own right. Marchand's "atypical" variety of choriocarcinoma may be mentioned here. Although in some cases the condition with this diagnosis was undoubtedly cancerous, we suspect that many other cases placed in this category because of the prevalence of giant cells were not in fact instances of cancer.

It seems clear that the presence of giant cells at any site is not a reliable criterion in assessing cancer.

In the removed uterus a trophoblastic node with its masses of trophoblast lying deep in the muscle gives unequivocal evidence of cancerous invasiveness. Only rarely, however, can curetted material show equally unequivocal evidence of invasion and muscle necrosis.

*Persistence of Trophoblast.*—There is no doubt that trophoblast persisting long after it should normally have disappeared may be of precancerous significance. If such persistent trophoblast is found and there is an associated clinical suspicion, choriocarcinoma is usually diagnosed. There is, however, the qualification that trophoblast may per-

46. Meyer, R.: Klin. Wchnschr. **46**:1162, 1909.

sist in association with hydatidiform or even normal villi for some months after cessation of pregnancy and yet have no precancerous significance. This fact was emphasized by Meyer [42] and was an important part of his diagnostic criteria.

### THE FAILURE OF HISTOLOGY

Nearly all of those who have studied choriocarcinoma from the standpoint of histology have come eventually to the conclusion that it is difficult, perhaps impossible, to predict the outcome from the histologic aspects alone. We were, however, impressed by the findings in our case 11, in which the original curettings, at a time when choriocarcinoma was not suspected, showed what would have been regarded as a highly cancerous neoplasm in any context. This was, however, the only such case in our series.

In table 4 there are recorded 23 cases in which the surgeon's opinion agreed with that of the histologist to the extent that he carried out hysterectomy. There were, however, a further 14 cases in which histologically there was an equally strong suspicion of choriocarcinoma but in which the clinical and other findings were not sufficient to justify hysterectomy. All the 14 patients have been traced; in none did choriocarcinoma develop and none died of choriocarcinoma.

### ORIGIN OF TROPHOBLAST

Trophoblast can be defined as a tissue, morphologically distinctive, with a constant hormonal accompaniment. Tissue satisfying this definition is found (*a*) surrounding the embedding ovum, and here considered by all embryologists to be fetal in origin; (*b*) in the trophoblastic hyperplasias, culminating in frank choriocarcinoma; (*c*) in teratomatous choriocarcinoma—for example, in the testis.

So far as the trophoblast in teratoma is concerned, it is only when a fetal origin is added to the definition of trophoblast that trophoblast-like tissue in the testis can reasonably be denied to be "trophoblast." If the host can produce trophoblast as defined in the foregoing paragraph, the question is: Is this resemblance accidental or is it due to causes of the same kind as those that act at the placental interface? The fact that such tissue is selectively associated with a hormonal disturbance similar to that of pregnancy makes an explanation in terms of coincidental morphology unlikely. In fact, it is necessary to postulate that the same stimuli which determine the morphologic character of fetal trophoblast at the placental interface arise and in some perverted way determine a similar morphologic development in trophoblastic hyperplasia of the uterus and in teratoma.

There is also the assumption, which has played so large a part in the study of choriocarcinoma, that the "malignancy" of choriocarcinoma is merely an excess of physiologic invasiveness.

For these reasons it seems worth while to discuss the development of trophoblast and the interrelationships of trophoblast and endometrium at the placental interface.

### EARLY IMPLANTING HUMAN OVA

There are several well illustrated accounts of previllous and early villous ova—Brewer and Fitzgerald,[47] Krafka,[48] Hertig and Rock,[49] and Hertig,[50] Davies [51] and many others.

In even the youngest of these ova—one of 7½ days' calculated age, Carnegie no. 8020, described by Hertig and Rock [49b]—nearly half the circumference has sunk into the endometrium, which means that there is no human ovum which can supply evidence of events taking place when the ovum actually makes first contact with endometrium.

### FREE BLASTOCYSTS

Schoenfeld [52] decided from his experiments that the free surface of a rabbit blastocyst did show trophoblastic "masses plasmodiales." Brachet [53] cultured free rabbit blastocysts and was of the same opinion. He went further in stating that even the beginnings of an ectoplacenta could be seen, though the accompanying drawings are not convincing. Further tissue culture experiments were made by Maximow.[54] He considered that explanted embryonic rabbit tissue was gradually penetrated and destroyed by proliferating trophoblastic cells: "The pictures sometimes show a striking resemblance to the chorio-epithelioma malignum. After six days of life in vitro only a vast trophoblastic syncytium may remain of the whole culture (fig. 32)." The appearance in this figure are not convincingly like those of a choriocarcinoma. Maximow also mentioned in this paper some of his earlier work, in 1900, when he, too, had concluded that the surface of a free blastocyst might show the beginnings of an ectoplacenta.

Clearcut trophoblastic behavior of this kind is not reported in free blastocysts described more recently by Pincus,[55] Heuser and Streeter [56a]

47. Brewer, J. I., and Fitzgerald, J. E.: Am. J. Obst. & Gynec. **34**:210, 1937.
48. Krafka, J., Jr.: Contrib. Embryol. **29**:169, 1941.
49. Hertig, A. T., and Rock, J.: (*a*) Contrib. Embryol. **29**:127, 1941; (*b*) **31**:65, 1945.
50. Rock, J., and Hertig, A. T.: Am. J. Obst. & Gynec. **44**:973, 1942.
51. Davies, F.: Tr. Roy. Soc. Edinburgh **61**:315, 1944.
52. Schoenfeld, H.: Arch. biol., Paris **19**:701, 1902-1903.
53. Brachet, A.: Arch. biol., Paris **28**:447, 1913.
54. Maximow, A.: Contrib. Embryol. **16**:47, 1925, p. 97.
55. Pincus, G.: J. Exper. Zool. **82**:85, 1939.
56. Heuser, C. H., and Streeter, G. L.: (*a*) Contrib. Embryol. **29**:15, 1941; (*b*) ibid., p. 26.

and Rock and Hertig.[57] Runner [58] and Fawcett, Wislocki and Waldo,[59] however, have cultured, in the anterior chamber of the eye in mice, recently fertilized ova removed from the oviducts; some autotransplants, others homotransplants made into either sex. Successful implants grew for as long as fifteen days or more. The inner cell mass was either suppressed or greatly retarded and abnormal in its development, but growth from the trophoblastic layer was constant. Morphologically this trophoblast seems to have been typical, although it tended to change into giant cells. It is to be noted that the trophoblast grew only for a limited period before degenerating, only in the presence of other tissue and only from fertilized ova which had presumably already been in contact with oviductal or uterine mucosa. This is the only evidence we have seen which affirms directly that trophoblast is derived from fetal cells, and altogether there is not much evidence that trophoblast can develop autonomously away from contact with maternal tissue.

### CONTACT OF BLASTOCYST AND ENDOMETRIUM

Detailed evidence about this can be found in the articles by Wislocki and Streeter [60a] and Heuser and Streeter [60b] on events as they occur in rhesus monkeys, in which development is traced from the very first contact of blastocyst and endometrium.

A pronounced proliferation of maternal epithelium begins in the macaque within a few hours after the embryonic pole of the blastocysts makes contact. This affects the superficial epithelium particularly, and the epithelium around the mouths of the nearest glands in lesser degree, resulting ultimately in formation of a well marked epithelial plaque. The formation of this plaque is no evanescent reaction, as it continues for a further seven to eight days before showing signs of degeneration. There is no quantitatively comparable reaction around human ova, but the principle is established that maternal epithelium is the tissue which shows the most striking morphologic and presumably purposive changes following contact of the ovum.

The cellular changes at the point of contact were well illustrated in the article of Heuser and Streeter.[60a] The authors described the process and stated that "in an otherwise unaltered uterine epithelium, cytolysis occurs at these contact points, and the responsibility for the cytolysis must be placed on the presence and activity of the invading trophoblasts."

57. Rock, J., and Hertig, A. T.: Am. J. Obst. & Gynec. **55**:6, 1948.

58. Runner, M. N.: Anat. Rec. **98**:1, 1947.

59. Fawcett, D. W.; Wislocki, G. B., and Waldo, C. M.: Am. J. Anat. **81**:413, 1947.

60. Heuser and Streeter [60]: (*a*) figs. 29 to 54; (*b*) figs. 48 to 52, particularly fig. 52; (c) 56.

The same article includes pictures of an 8 to 9 day ovum which show that directly under the embryonic node at this time the uterine epithelium is unaltered, while at its margins are appearances described by the authors as a massive engulfing of nuclei by trophoblast on one side and as a more gradual descending of nuclei into trophoblast on the other side. The subsequent fate of this block of as yet unaffected epithelium is interesting.

Heuser and Streeter stated [54b] that on the tenth day the thickened trophoblastic wall of the embryonic pole of the ovum is found to be exactly occupying the area where there had hitherto been uterine epithelium. That is to say, in a period of some twenty-four hours a block of maternal epithelium has been completely removed and replaced by trophoblast which is now in contact with endometrial stroma. It seems that there is no appreciable transitional stage; according to the authors, in the process " . . . an abrupt change has been made from maternal tissue to fetal tissue . . . "

During this time the epithelium in the immediate neighborhood has been stimulated into active proliferation both on the surface and around the necks of adjacent glands. Dark areas in the epithelium [60c] are interpreted by the authors as indicating cytolysis at points of contact with the trophoblast. It does appear, however, that there are much wider areas where the tissue described as trophoblast and maternal epithelium merge with no comparable indication of cell damage, and we wondered whether a proportion of the cellular area directly under the embryonic node could now, at the tenth day, perhaps just as well be proliferating maternal epithelium as trophoblast of fetal origin. In other words, was there possibly no abrupt changeover, much of the tissue concerned being maternal epithelium all the time? At any rate this tissue appears closely similar to tissue illustrated as proliferating maternal epithelium in some of the other illustrations.

In connection with one of the illustrations mentioned in a foregoing paragraph Heuser and Streeter made the following remark [54b]: "In figure 49 . . . one can see a segment of epithelium just before its disappearance and replacement by *or conversion into* trophoblastic syncytium" (our italics). We do not know how much significance to give to this statement. It was probably not meant to carry the full implication it could have, but we draw attention to it here as a statement to be thought about.

In the macaque the epithelial plaque continues to grow for some seven to eight days, until degenerative changes appear. This happens soon after the appearance of the chorionic villi, which grow outward into the plaque and replace it completely. While degenerating, the epithelium forms large numbers of multinucleated syncytial masses well shown on plates 8 and 12 of the article of Wislocki and Streeter.[35a]

Second hand lay impressions must be interpreted cautiously, but one does get an impression of cellular confusion at the time of contact, and

of the difficulty after a time of knowing the origin of the cells at the junctional zone.

*Endometrial Reaction.*—This is seen in a "pure" form in deciduomas.

Deciduomas are tumors of the endometrium, sometimes predominantly stromal, sometimes (as in the macaque) predominantly epithelial, produced by artificial stimulation of the luteinized endometrial surface as, for example, by scratching, insertion of a ligature or contact of an active electrode.

Their formation was first studied in detail by Loeb [61] in the guinea pig. Similar experiments have been carried out since then on many species of animal, for example, rabbits by Hammond,[62] Klein [63] and Mossman [37a]; rats by Selye and McKeown [64a] and Krehbiel [65]; mice by Atkinson,[66] and Macaque by Hisaw,[67] Hisaw, Greep and Fevold [68] and Rossman.[69]

The results obtained by all these workers agree closely. The tissue changes produced are very similar to, and in some instances practically indistinguishable from, those seen in normal pregnancy. Wislocki and Streeter [35a] observed that the masses of multinucleated giant cells and clumps of syncytium formed by the degenerating epithelial plaque in the pregnant macaque were practically indistinguishable histologically from the same kind of cell formations found in degenerating deciduomas by Hisaw.[67] Mossman [37a] also stressed the similarity between deciduomatous and pregnancy reactions and described how glass beads or wax pellets implanted in the endometrium in animals caused formation of a chamber resembling in many ways a true pregnancy implantation cavity. Wislocki, Dempsey and Fawcett [70] have referred to such implantation experiments and stressed the occurrence of species differences.

There is no mention of structures specifically resembling trophoblast, and illustrations of the process do not show any typical trophoblast complete with syncytial streamers or *Balkenwerke*. On the other hand, when there are large sheets of epithelial cells, some fused and multinucleated as in macaque deciduomas there is a picture not very different from that of a mass of Langhans' cells, certainly as seen in choriocarcinoma.

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61. Loeb, L.: J. A. M. A. **50**:1897, 1908.
62. Hammond, J.: Proc. Roy. Soc. London (s. B) **89**:534, 1915-1917.
63. Klein, M.: Arch. d'anat., d'histol. et d'embryol. **18**:1, 1934.
64. Selye, H., and McKeown, T.: (*a*) Proc. Roy. Soc. London (s. B) **119**:1, 1936; (*b*) ibid., p. 25.
65. Krehbiel, R. H.: Physiol. Zool. **10**:212, 1937.
66. Atkinson, W. B.: Anat. Rec. **88**:271, 1944.
67. Hisaw, F. L.: Anat. Rec. (supp.) **64**:54, 1935.
68. Hisaw, F. L.; Greep, R. O., and Fevold, H. L.: Am. J. Anat. **61**:483, 1937.
69. Rossman, I.: Am. J. Anat. **66**:277, 1940.
70. Wislocki, G. B.; Dempsey, E. W., and Fawcett, D. W.: Obst. & Gynec. Surv. **3**:604, 1948.

These deciduoma experiments indicate clearly that the endometrium is an active, perhaps a dominantly active, participant in placentation. On general grounds one would certainly expect the endometrium to behave in a protective, nutritive and maternal way rather than as the passive site of attachment of an invading parasite. Since it has to serve the functions of a whole organism one would expect these different functions to elicit the varied morphologic developments which in fact there are in the pregnant endometrium.

### MECHANISM OF IMPLANTATION

According to de Gouvêa,[71] Hensen[72] was the first to attribute an active role to the mammalian egg in implantation through tissue corrosion. There must be few, if any, accounts since then of early implantation and placentation which do not include somewhere the word "invasion" or "invasiveness" with all its connotation of destructive, aggressive and cancerous behavior.

The chain of events which starts with sexual attraction, includes the embedding of an ovum and ends with parturition is a most orderly and designed physiologic process. It would be quite extraordinary if it depended for its success on a destructive, corrosive action of the ovum—"physiological malignancy," "the kiss of death for the endometrium"—which continued until some defensive circumvallation was hastily and belatedly thrown up by the mother at the endometrial surface. Such anthropomorphic metaphors are quite strained in describing any physiologic process. Even with the most benign mergence there must be some histologic changes at the interface.

This concept of "invasiveness" has done much to distort and falsify the interpretation of changes at implantation, and there is, in fact, a growing tendency to draw away from the idea of lytic corrosion as the principal mechanism of implantation (Mossman[27a]).

*Hemorrhage.*—The observation that free blood is constantly associated with trophoblast, both adjacent to the ovum and in choriocarcinoma, has long been considered "proof" of the invasiveness of trophoblastic cells. Two comments can be made. First: Free bleeding is found in the posterior chamber of the eye of the mouse as part of the response to an ovum cultured in, and still confined to, the anterior chamber (Fawcett, Wislocki and Waldo[60]). That is, the hemorrhage here at least is not due to actual cellular invasion of blood vessel walls. Second: Selye and McKeown,[64b] as a result of their observations on deciduomas in rats, have stated:

> . . . In artificially produced deciduomata a large blood sinus forms at a certain stage of development by liquefaction of the decidual cells between the blood

71. de Gouvêa, J. N.: Gynécologie **9**:498, 1904.

72. Hensen: Ztschr. f. anat. u. Entwcklngsgesch., 1878; cited by de Gouvêa.[71]

vessels. This large blood sinus is analogous to the inter-villous space of the placenta. Its formation in the absence of any foetal tissue shows the ferments of the chorionic villi not to be essential to the opening of maternal blood vessels.

A similar statement, with illustration, is made by Selye.[73a]

*Necrosis.*—Caturani [73b] stated that " the old conception of the formation of the decidual chamber out of a circumvallation of the uterine mucosa" received a severe blow through the demonstration of a zone of uterine necrosis around the ovum described by Bryce and Teacher.[74] It is now realized that this was a pathologic ovum.

Recent observations suggest that the necrotizing properties of embedding trophoblast have been greatly overemphasized. Comments to this effect have been made by Krehbiel,[66] Wislocki and Streeter [85a] and Davies.[51] If necrosis of maternal tissue is to be subtracted from the appearance of "invasiveness," it is difficult to see how the residual picture is to be distinguished from a physiologic mergence.

The details of the mechanism of embedding have been investigated by many workers, for example Brewer and Fitzgerald [47] and Mossman.[67] In general it can be said that such explanations have not got far beyond the statement that an ovum embeds and grows in maternal tissue. The ovum must implant, and must expand, and must occupy the space previously occupied by maternal tissue. There must, therefore, be readjustment of cells and disappearance of cells. "Necrosis" and "invasiveness" are quite inappropriate words in descriptions of a determined, purposive physiologic process.

## SUMMARY

Three impressions can be derived from an examination of accounts of the processes involved in the embedding of the ovum: (1) the cellular confusion at the time of implantation, and the difficulty of recognizing the origin of individual cells and tissues; (2) the important part played by the maternal tissues; (3) the inappropriateness of the word "invasiveness."

## NONGESTATIONAL CHORIOCARCINOMA

Many reported cases of choriocarcinoma can be placed in the category of nongestational choriocarcinoma. They can be divided into three groups: (1) choriocarcinoma occurring in a man or in an undoubted virgin at some site other than the usual sites for teratoma; (2) choriocarcinoma occurring in a possibly fertilized woman at some site other than the fallopian tubes, the uterus or the vagina in the absence of any

73. Caturani, M.: (*a*) Am. J. Obst. **75**:591, 1917; (*b*) ibid., p. 593.

74. Bryce, T. H., and Teacher, J. H.: In Contributions to the Study of the Early Development and Imbedding of the Human Ovum, Glasgow, 1908, p. 7.

apparent tubal or uterine pregnancy and apparently not in association with teratoma; (3) choriocarcinoma occurring in a person of either sex at any site where teratoma is known to develop.

Group 1, so far as our reading has gone, includes 3 cases only—that of Maizels[75] of choriocarcinoma occurring in a 71 year old virgin; that of Weinberg,[76] in a 70 year old man (bladder), and that of Stoy,[77] in a 40 year old man (liver).

In group 2, unless proof of virginity is absolute, the validity of the cases obviously depends on how much credibility is given, first, to the capacity of choriocarcinoma for latency of development, and second, to the likelihood of a primary uterine or tubal choriocarcinoma disappearing spontaneously (see later comment). Reviews of cases of this kind have been published by Berman[78] and Resnick.[79]

In most of these cases in groups 1 and 2 the diagnosis is mainly dependent on the histologic picture. This means that criticism must be based on photomicrographs, which are at best a poor substitute for the sections. For that reason the cases cannot be criticized individually, although it might be suspected that opinions could differ on some of them. One may say only that the human population is large; the tumors in many sites have a wide and varied morphologic character and selected microscopic fields an even wider variability; that women apart from those with tumors may have abortions, retained products of conception, and positive Aschheim-Zondek reactions; that the urines of elderly men, postmenopausal women and castrates of either sex may produce positive Aschheim-Zondek reactions of appearance 1 type; that the threshold for publishing a case varies, and that actuarially one would expect from time to time scattered cases of tumor with morphologic and hormonal aspects somewhat similar to, but not really those of, choriocarcinoma. During a large proportion of reproductive life the urines of many women will produce positive Aschheim-Zondek reactions.

Group 3 includes cases of choriocarcinoma of the testis (Fortner and Owen,[80] for instance, and many others in the literature); less commonly in the ovary (see de Zalka[81] for many references), and rarely in the mediastinum (Emrys-Roberts and Hall[82]; Hirsch, Robbins and Hough-

75. Maizels, G.: Lancet **1**:690, 1940.
76. Weinberg, T.: Am. J. Path. **15**:783, 1939.
77. Stoy, R.: Inaug. Dissert., Frankfurt, 1921; cited by de Zalka.[81]
78. Berman, L.: Am. J. Cancer **38**:23, 1940.
79. Resnick, L.: J. Obst. & Gynaec. Brit. Emp. **52**:180, 1945.
80. Fortner, H. C., and Owen, S. E.: Am. J. Cancer **25**:89, 1935.
81. de Zalka, E.: Am. J. Path. **4**:59, 1928.
82. Emrys-Roberts, E., and Hall, I. W.: J. Path. & Bact. **14**:135, 1910.

ton [83]), retroperitoneal region (Ritchie [84]; Erdmann, Brown and Shaw [85]), and pineal region (Stowell, Sachs and Russell [86]).

### CHORIOCARCINOMA TESTIS

For purposes of discussion choriocarcinoma testis can be taken as the type example of group 3. There are two views as to its origin—that the trophoblastic structure is an accident of morphologic development, and that the tissue is truly trophoblast. It certainly seems that the argument has arisen not because the tissue does or does not resemble gestational choriocarcinoma but because the resemblance is so close that the identification would raise many difficult questions.

The question whether choriocarcinoma testis is a chance and unusual variant such as any disease will throw up on its borders, or whether it has sufficiently distinctive features to rank as a separate entity is not relevant here. The point is: How closely does it resemble gestational trophoblast?

Accidental morphologic resemblance to trophoblast will not explain the selective incidence of such resemblances in the gonads and in teratoma. It is also true, admittedly, that such resemblances occur only in small areas of the tumor—those which tend to be illustrated. It does seem, whatever its significance, that some tumors of the testis do show a structure, even if only in places, identical with that seen in gestational choriocarcinoma.

It often happens that when trophoblast is found in the testis there are also present other types of tissue of apparently equal significance, the whole adding up to teratoma testis. If undifferentiated teratomatous cells can develop into glia, cartilage, entoderm and indeed any tissue formed by division of the fertilized ovum, there is no reason why there should not develop trophoblast of the same generation, parentage and genetic constitution and derived from the same fertilized ovum. When, in a teratoma, there is tissue morphologically resembling adult cartilage, it is called "cartilage" for that reason, derived by implication from cartilage precursor cells. The same argument must apply to tissue morphologically resembling trophoblast. It is quite illogical to dismiss tissue undoubtedly resembling trophoblast as not being trophoblast for no other reason than that calling it trophoblast would identify it with another tissue which is itself defined by morphology. The question is: Is this tissue of a different genetic constitution from that of the host or is it not?

83. Hirsch, O.; Robbins, S. L., and Houghton, J. D.: Am. J. Path. **22**:833, 1946.

84. Ritchie, J.: J. Obst. & Gynaec. Brit. Emp. **4**:65, 1903.

85. Erdmann, J. F.; Brown, H. A., and Shaw, H. W.: Urol. & Cutan. Rev. **45**:1, 1941.

86. Stowell, R. E.; Sachs, E., and Russell, W. O.: Am. J. Path. **21**:787, 1945.

There are four possible answers:

1. *Testicular and gestational choriocarcinoma resemble each other fortuitously.*

This has just been discussed.

2. *The same factors, whatever they may be, act equally on fetal trophoblast in the uterus and on hostal tissue in the testis to produce tumors with the same morphologic aspect and behavior.*

That is, such differences as may exist between homologous and autologous tumors would not be reflected in the morphologic aspect and behavior of choriocarcinoma at either site. Alternatively, so far as gestational choriocarcinoma owes its peculiar qualities to its peculiar origin as the only homologously transplanted human tumor, this peculiarity of origin, since it is absent, would not explain the behavior of choriocarcinoma of the testis. (The question of a mutational cause of cancer in general will not be discussed here.)

3. *Gestational choriocarcinoma arises from fetal trophoblast and choriocarcinoma testis arises also from "fetal" trophoblast, or at least from cells of a genetic constitution different from that of the host.*

If choriocarcinoma testis is identical with gestational choriocarcinoma, its cells will stand in relation to the host in some such similar relation as child to parent (or binovular twin to twin) i. e., genetically distinct. This immediately raises the question of how such cells have been formed —mutation, perhaps, or parthenogenesis. The prospect of having to invoke some such *outré* explanation must have been responsible for much of the disinclination to accept choriocarcinoma testis as an entity.

4. *Choriocarcinoma testis, like chondroma testis, and choriocarcinoma uteri are both genetically identical with their hosts.*

If gestational trophoblast were not of fetal origin, the fourth explanation would be so obvious that discussion on it would be no more necessary than in deciding that tissue resembling glia in teratoma is glia. There is no doubt that in many instances of testicular choriocarcinoma, certainly in several of our sections, characteristic "trophoblast" merges imperceptibily with areas of indifferentiated epithelial tissue whose hostal origin would never be questioned.

Assuming that physiologic trophoblast is undoubtedly fetal in origin, there remains the choice between the second and third explanations, i. e., either that teratomatous trophoblast is fetal and genetically distinct or that hostal tissues, given the appropriate stimulus, can form tissue morphologically resembling trophoblast. We ourselves would say that the latter is the less unlikely choice.

(*To Be Continued*)

# Notes and News

**Lectures on Growth and Cancer.**—A series of monthly meetings on problems of growth and cancer will be presented throughout the winter by the department of pathology of the University of Vermont College of Medicine, Burlington, Vt., at 8 p.m., in the Fleming Museum. The speakers and their subjects are as follows: December 2, Dr. Charles B. Huggins, University of Chicago, "Serum Proteins in Cancer"; Jan. 5, 1950, Dr. Leonell C. Strong, Yale University School of Medicine, "Genetics and Cancer"; February 9, Dr. Albert Tannenbaum, Chicago, "Diet and Cancer"; March 2, Dr. Van R. Potter, University of Wisconsin Medical School, "Enzymes, Growth and Cancer"; March 30, Dr. Roy Hertz, National Cancer Institute, "Vitamin-Hormone Interrelationships Affecting Tissue Growth," and May 4, Dr. Robert E. Stowell, University of Kansas School of Medicine, "Nucleoproteins, Growth and Cancer."

**Conference on Histochemistry.**—A meeting is being planned for the consideration of the histochemical methods and the extent to which they may be applied in the fields of anatomy, pathology, biochemistry, endocrinology, bacteriology and other disciplines. This conference has been scheduled for March 25, 1950 in the University of Pennsylvania Department of Anatomy, Philadelphia. Further information will be supplied on request by the acting secretary, R. D. Lillie, M.D., Laboratory of Pathology and Pharmacology, National Institutes of Health, Bethesda 14, Md.

**Deaths.**—Paul Allen Wheeler, associate professor of pathology at Baylor University College of Medicine and formerly assistant professor of pathology at the Washington University School of Medicine, St. Louis, died in Rochester, Minn. on October 1, aged 46, of periarteritis nodosa.

***Hygeia* Renamed.**—The trustees of the American Medical Association have authorized the renaming of the Association's health magazine, *Hygeia*. The new name will be *Today's Health*. The change will be made with the issue of March 1950.

**Appointments.**—Dr. Lee N. Foster, pathologist at the Lawson Veterans Hospital, has been promoted from associate in pathology to assistant professor of pathology at Emory University School of Medicine.

Dr. Ernst Loeffler, associate professor of pathology in Loyola Dental School, Chicago, died suddenly on September 24 last from coronary thrombosis while working as research associate in the Hektoen Institute of the Cook County Hospital. He was for a time associate pathologist in the Mount Sinai Hospital and had charge of pathology in the Cook County Hospital from 1944 to 1946. He worked hard to do justice to the material there under war conditions. He came to Chicago in 1938 from Vienna, Austria, where he served under Professor Erdheim.

Dr. Francis D. Speer has been appointed professor of pathology and clinical pathology and director of the department of pathology at New York Medical College, to succeed Dr. George K. Higgins, resigned.

Dr. William V. Hare has been appointed professor of pathology and chairman of the department of pathology at the University of Mississippi School of Medicine.

# Books Received

EARLY CARCINOMA OF THE UTERINE CERVIX: PATHOGENESIS AND DETECTION. By Hansjakob Wespi, M.D., chief of the Obstetrical and Gynecological Department, Frauenfeld Hospital, Aarau, Switzerland. Translation by Marie Schiller, Ph.D. Foreword and Survey by Walter Schiller, M.D. Revised and augmented edition. Pp. 271 with 95 figures. Price, $6.50. Grune and Stratton, Inc., 381 Fourth Avenue, New York 16, 1949.

The general contents of this monograph are aptly described by the title. Major emphasis is placed on colposcopic diagnosis and the iodine test. A few comments are made on the cytologic smear method of Papanicolaou, of which the author has made limited use. The changes in the cervix visualized with the colposcope at a magnification of 12 diameters are described in detail. An attempt is made to trace their interrelationships and the stages by which they may progress to cancer. The author recognizes the following changes: simple atypical epithelium, irregular epithelium, increasingly atypical epithelium and surface carcinoma. These changes are illustrated with a series of excellent photomicrographs. A lengthy bibliography and an index complete the volume.

The author has made a significant contribution to knowledge of the genesis of early carcinoma of the cervix by following patients with different types of lesions over long periods and observing the ultimate outcome. Unfortunately, in some categories his series of cases is small, and so the conclusions are of limited value. The author presents data bearing on the subsequent behavior of minimal lesions and on the question of when they are and are not cancers. Since this is today one of the foremost problems confronting gynecologists and pathologists, his statement, illustrated by case reports, that the increasingly atypical epithelium does not necessarily become cancer appears important. It is obvious that the borderline between benign changes and true surface carcinoma or carcinoma in situ is not yet clear, either on clinical or on microscopic examination; hence cancer may be overdiagnosed.

The book unfortunately has a number of drawbacks. There is some evidence of repetition and labored argument and of poor organization of material and section headings. Some new terms are introduced without definition—for example, the various "Cols." The translation is adequate but inelegant; since it is literal, much of the phrasing remains foreign. There are a number of misspellings. The word *Belag* is not translated; it is suggested that "covering" might be adequate.

The book is of value mainly to gynecologists, but pathologists and personnel of cancer detection centers will find in it useful information and a model in detailed study of cases.

STREPTOMYCIN: NATURE AND PRACTICAL APPLICATION. Edited by Selman A. Waksman. Pp. 618. Price, $10. Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, 1949.

Under the leadership of Dr. Waksman, there has emerged a well printed, substantially bound compilation of much of the knowledge pertaining to streptomycin up to the latter part of 1948. This is a timely and useful summation

of pertinent information, covering a wide field of interests. Included in appropriate sections are relevant data on dihydrostreptomycin.

The volume consists of 46 chapters, written by 59 contributors, many of whom were identified with the various aspects of the development of the knowledge of streptomycin soon after Dr. Waksman and his associates announced the discovery of the antibiotic. For this reason the majority of the points of view are based on data observed at "first hand." This fact lends to the content of this book an unusual amount of the virtue of authenticity.

The subject matter is divided logically into four sections. The first section pertains to historical, microbial and chemical aspects of streptomycin. The second is concerned with the activity of streptomycin, in vitro and in vivo, against a wide variety of pathogenic micro-organisms. The third section, consisting of 267 pages, is devoted to the clinical uses of streptomycin, which has been tested in the treatment of a variety of diseases, including tuberculosis, tularemia and plague. The final section of the book is devoted to certain miscellaneous uses of streptomycin, as in the isolation or recovery of viruses, in veterinary medicine and in the control of bacterial diseases of plants. Further ways in which the drug might be used in the control of diseases of animals and plants are suggested. Much additional work is desirable in these fields, however, before the value and the limitations of streptomycin are fully established. An important feature of the book is the bibliography which follows each chapter except two. That bibliographies are omitted in these instances is regrettable, and the reasons are not apparent. It it unfortunate that the index is not more adequate. The index contains errors and is not sufficiently comprehensive to direct the reader to many important subjects in the text.

This book is an important and useful summation of the developments by which streptomycin has become a practical weapon in the attack on certain infectious diseases. Bacteriologists, experimentalists and practicing physicians should be grateful to Dr. Waksman for having made available in a single volume such an abundance of authoritative information concerning this important antibiotic.

THE TEMPORAL BONE AND THE EAR. By Theodore H. Bast, Ph.D., professor of anatomy, University of Wisconsin, Madison, Wis.; Barry J. Anson, M.A., Ph.D., professor of anatomy, Northwestern University Medical School, Chicago. Pp. 478, with 165 illustrations. Price, $12. Charles C Thomas, Publisher, 321-327 East Lawrence Avenue, Springfield, Ill., 1949.

In this volume of 448 pages the authors have brought together their extensive original researches into the embryonal development of the ear. The authors advocate a new nomenclature for the parts of the internal ear. The term "otic labyrinth" refers to the structures derived from the primitive otic vesicle—that is, the epithelium-lined ducts and cavities comprising the membranous or endolymphatic labyrinth of textbooks of anatomy. The fluid within the otic labyrinth is called the "otic fluid" and corresponds to the endolymph of the textbooks. The terms "periotic fluid" and "periotic labyrinth" refer to the perilymph and all the soft tissue structures outside the otic labyrinth and contained within the bony labyrinth. The term "otic capsule" is used to refer to the bony labyrinth of the textbooks. This new nomenclature is logical and simple and avoids some of the confusions from the older terms.

The major portion of the text is devoted to a complete and detailed description of the development of the otic labyrinth, the periotic labyrinth and the otic capsule, based on the original researches of the authors. Many excellent illustrations help the student to visualize the various stages in the development of these structures.

Of particular interest to the practicing otologist is chapter V, "Histological Variations and Pathological Processes," in which the authors describe the abnormal cartilage masses observed in the region of the fissula ante fenestram which may later ossify into a callus-like bone representing the beginning of otosclerosis.

The concluding chapter, "A Historical Survey of the Internal Ear," contains a fascinating account of the theories of balance and hearing from the early Greeks down to the present day.

This book will become an authoritative standard reference work on the development of the ear. There is an excellent subject index and a very complete author index.

PATHOLOGY AND SURGERY OF THYROID DISEASE. By Joseph L. DeCourcy, M.D., senior surgeon, Good Samaritan Hospital; director, DeCourcy Clinic, Cincinnati, and Cornelius B. DeCourcy, M.D., member, DeCourcy Clinic Surgical Staff, Cincinnati. Pp. 478, with 94 illustrations. Price, $10. Charles C Thomas, Publisher, 321-327 East Lawrence Avenue, Springfield, Ill., 1949.

The authors have reviewed the thyroid gland in the light of an extensive clinical experience and of recent knowledge of the anatomic, histologic, physiologic, pharmacologic and pathologic aspects of the organ. A sound and detailed type of preoperative preparation of the patient has been outlined, including the relative merits of iodine, thiouracil and propylthiouracil in the production of a recession of thyrotoxicosis. They take the justifiable stand that regardless of improvement made by medical management, surgery nevertheless remains the surest approach to permanent remissions or cures.

There are special chapters on Riedel's struma, thyroid disease of later life, thyroiditis and the hypothyroid status. The relative importance of local intratracheal inhalation and intravenous and spinal anesthesia are well evaluated.

In a discussion of operative treatment, the technic has been somewhat oversimplified in the illustrations, which might lead the inexperienced operator to underestimate the difficulties of the procedure.

The authors still advocate preliminary ligation of thyroid arteries in a higher percentage of cases than now appears necessary with modern preoperative pharmaceutic management of blood transfusion at the disposal of the surgeon.

On the whole, the book gives an excellent and balanced summary of the present status of thyroid disease, and should be helpful to both surgeons and interns.

THE PHARMACOLOGY AND TOXICOLOGY OF URANIUM COMPOUNDS: WITH A SECTION ON THE PHARMACOLOGY AND TOXICOLOGY OF FLUORINE AND HYDROGEN FLUORIDE. Edited by Carl Voegtlin, Ph.D., formerly chief of the Division of Pharmacology, National Institute of Health, United States Public Health Service, and formerly director of cancer research and chief of the National Cancer Institute; and Harold C. Hodge, Ph.D., professor of pharmacology and toxicology, University of Rochester School of Medicine and Dentistry. National Nuclear Energy Series, Division VI, Volume 1. Two volumes. Pp. 1084. Price, $10. McGraw-Hill Book Company, Inc., 320 West Forty-Second Street, New York 18, 1949.

These two volumes are a compilation of the data from a large number of experiments carried out at the University of Rochester between 1943 and 1945 and cover a wide variety of studies of uranium compounds from the standpoints of pharmacology and toxicology. Studies on the chemistry of uranium compounds are included. The topics covered are: analytical methods; symptoms of poisoning and pathologic observations; toxicity by injection, ingestion, percutaneous appli-

cation, intraocular administration and inhalation; distribution and excretion; tolerance, and biochemical effects and possible mechanism of action.

From the standpoint of the value of these volumes as general reference books, their principal disadvantage is the profusion of experimental detail, much of which could have been eliminated without detracting from their usefulness. Indeed, some chapters read as though they were merely diaries of the progress of the investigation rather than well organized presentations of the pertinent findings.

Probably the most valuable single contribution is the introduction by Harold Hodge, who has masterfully synthesized the essential points of each subject into a highly readable and intelligible summary.

MEDICAL ETYMOLOGY: THE HISTORY AND DERIVATION OF MEDICAL TERMS FOR STUDENTS OF MEDICINE, DENTISTRY, AND NURSING. By O. H. Perry Pepper, M.D., professor of medicine, University of Pennsylvania. Pp. 263. Price, $5.50. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, 1949.

This is a fascinating little volume which contains a vast amount of information in its 237 pages of text. Preclinical and clinical subjects are arranged more or less in the orderly sequence in which the medical student encounters them. Within each subject, the words in common usage are arranged alphabetically and their derivations indicated. There is an excellent chapter on the background of medical terminology, and throughout the text there are innumerable historical references and not infrequently anecdotes and witticisms. Our medical heritage, so varied and so rich, stemming as it does from the dawn of history, is readily reflected in a unique text of this kind. The printing and the arrangement of this volume are excellent. There is an index of all the words included in the text, which facilitates rapid reference. It can be highly recommended to medical students and teachers—for the former it will promote the acquisition of a large and new vocabulary, and for the latter it will enrich medical teaching.

GENERAL PATHOLOGY AND PATHOLOGICAL ANATOMY: SECTION V OF EXCERPTA MEDICA. A monthly abstracting service of articles from every available medical journal in the world comprising 15 sections and covering the whole field of clinical and experimental medicine, under the general editorship of M. W. Woerdeman, M.D., F.R.N.A.S., professor of anatomy and embryology in the University of Amsterdam, chairman, and A. P. H. A. De Kleyn, M.D., F.R.N.A.S., professor of oto-, rhino-, laryngology in the University of Amsterdam, and W. P. C. Zeeman, M.D., emeritus professor of ophthalmology in the University of Amsterdam, members. Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, 1949.

All articles dealing with morphologic pathology are covered in this section. Separate subdivisions are devoted to forensic pathology, comparative pathology, geographic pathology, gerontologic pathology and pediatric pathology.

INTRODUCTION TO PARASITOLOGY WITH SPECIAL REFERENCE TO THE PARASITES OF MAN. By Asa C. Chandler, M.S., Ph.D., professor of biology, Rice Institute, Houston, Texas; formerly officer-in-charge, Hookworm Research Laboratory, School of Tropical Medicine and Hygiene, Calcutta, India. Eighth edition. Pp. 618. Price, $6. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, 1949.

For more than thirty years a popular student textbook, it is now completely revised, with improved and new illustrations.

BONE AND JOINT RADIOLOGY. By Emerik Markovits, M.D., formerly scientific collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht Institut), Vienna; head of the Radiologic Department of Elizabeth Hospital of the City of Budapest; postgraduate lecturer at the Central Radiologic Institute of the University of Budapest; radiologist of the Steiner Cancer Clinic, Atlanta, Ga. Pp. 446, with 616 illustrations. Price, $20. The Macmillan Company, 60 Fifth Avenue, New York 11, 1949.

As the title suggests, this book is addressed primarily to the radiologist. It is liberally illustrated with roentgenograms and fine line drawings. The mechanisms responsible for the structural features of each process are briefly referred to in most instances, but detailed descriptions are not included. Data for making differential diagnoses on radiologic grounds are set forth in numerous concise tables.

The book has a simple, direct and orderly approach to the problem of interpretation of roentgenograms of the osseous system and will be a valuable reference work in the libraries of radiologists. In addition, physicians interested in diseases affecting bone and articular structures will find it valuable.

MORGAGNI'S SYNDROME: HYPEROSTOSIS FRONTALIS INTERNA, VIRILISMUS, OBESITAS. By Folke Henschen, M.D., Stockholm, Sweden. Emeritus professor of pathology at the Caroline Institute. Pp. 172, with 99 illustrations. Price 30 shillings. Oliver & Boyd, Ltd., Tweeddale Court, 14 High Street, Edinburgh, Scotland; 98 Great Russell Street, London, W.C.1, England, 1949.

This small volume describes a triad of symptoms, hyperostosis frontalis interna, virilism and obesity, for which the author in 1936 proposed the fitting name Morgagni's syndrome. The monograph is based on a study of 1,000 skulls from female subjects examined at necropsy and an examination, for control purposes, of an equal number of skulls from persons of the male sex. The findings are clearly stated and illustrated. Tables and diagrams are skillfully used to summarize the pertinent data. Pathologists, radiologists and anatomists, who frequently encounter the first member of the triad of Morgagni's syndrome, will find this monograph an invaluable aid to an understanding of this remarkable lesion. Clinicians, particularly those concerned with endocrinologic problems, and students of medicine will be interested in it.

ATLAS OF NEUROPATHOLOGY. By William Blackwood, M.B., F.R.C.S.E., assistant pathologist, National Hospital, Queen Square, London; T. C. Dodds, F.I.M.L.T., F.I.B.P., F.R.P.S., laboratory supervisor, University of Edinburgh Department of Pathology, and lecturer to the Society of Radiographers (Fellowship Course, Scottish Branch); and J. C. Sommerville, A.I.M.L.T., senior technician, University of Edinburgh Department of Neuropathology, and Scottish Mental Hospitals' Laboratory. Foreword by Prof. A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E., professor of pathology, University of Edinburgh. Pp. 199, with 262 illustrations. Price, $9. Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 5, 1949.

This atlas is based on demonstrations which have been made for many years in the study of neuropathology in Scottish mental disease hospitals and in the University of Edinburgh. It presents the most important neuropathologic conditions clearly and simply and will be of great help to clinicians and pathologists beginning the study of neuropathology.

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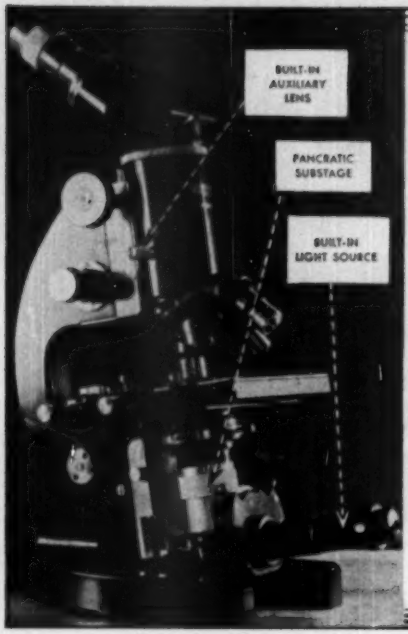


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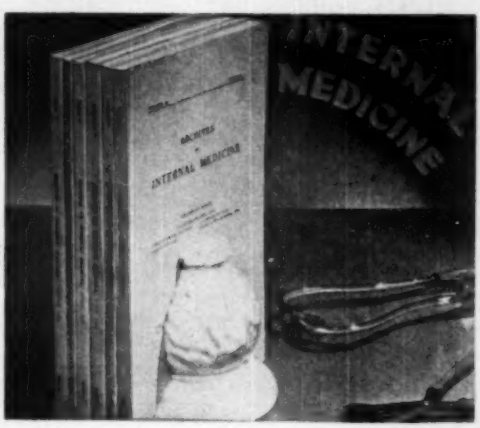


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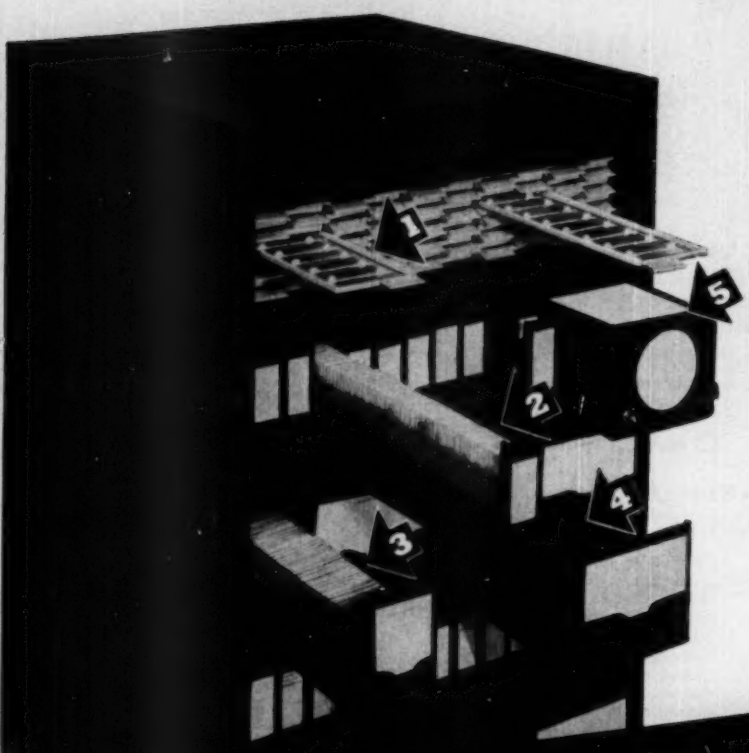


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